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Fetal cerebral vascular impedance is abnormal in left congenital diaphragmatic hernia

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Abstract

Objectives: Congenital diaphragmatic hernia (CDH) can cause significant mass effect in the fetal thorax displacing the heart into the opposite hemithorax. In left CDH (L-CDH), this is associated with smaller left-sided cardiac structures and lower left ventricular cardiac output (LVCO). The effect of these physiologic changes on cerebral blood flow is not well understood. We sought to describe the middle cerebral artery pulsatility index (MCA PI), a measure of vascular impedance, in L-CDH and right CDH (R-CDH) versus unaffected fetuses, and the relationship of MCA PI to LVCO. We hypothesized that MCA PI is lower in L-CDH and similar in R-CDH compared to controls. We further hypothesized that MCA PI would be correlated with LVCO.

Methods: We identified all fetuses with CDH at UCSF from 2011 to 2018. Fetal echocardiograms and ultrasounds were reviewed. Umbilical artery (UA) and middle cerebral artery (MCA) Dopplers were measured to calculate pulsatility indices. Ventricular outputs were calculated using Doppler derived stroke volume and fetal heart rate. Lung-to-head ratio (LHR), estimated fetal weight, biparietal diameter (BPD) and head circumference (HC) were obtained from fetal sonograms. A subset of survivors had data available from neurodevelopmental assessments as measured by the Bayley Scales of Infant Development-3rd edition. Measurements in CDH fetuses were compared to unaffected, gestational age-matched controls.

Results: A total of 66 fetuses (L-CDH= 53; R-CDH= 11) comprised the study cohort, with 27 unaffected fetuses serving as controls. Mean gestational age at evaluation was similar in all three

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groups. Compared to controls, fetuses with L-CDH had significantly lower MCA PI z-scores (−1.3, 95% CI: −1.6, −1.0; control: 0.08, 95% CI: −0.5, 0.6, p <0.001), while there was no difference when compared to the R-CDH group. There was a strong positive association between LVCO and MCA PI z-score (p= 0.01). BPD and HC were similar in all three groups. At follow up, mean cognitive and language scores in the CDH group were within one standard deviation of the general population.

Conclusion: MCA PI values are significantly lower in L-CDH fetuses as compared to controls and a lower LVCO was correlated with lower MCA vascular impedance. The neurodevelopmental effect of changes in MCA PI in response to decreased LVCO are unknown, although all survivors that underwent testing in this cohort scored in the normal range.

Keywords

congenital diaphragmatic hernia; middle cerebral artery pulsatility index; cerebrovascular resistance; cerebral sparing; neurodevelopment

INTRODUCTION:

Congenital diaphragmatic hernia (CDH) can cause significant mass effect in the fetal thorax displacing the heart into the opposite hemithorax with resultant redistribution of cardiac blood flow in the fetus[1–2]. In left CDH (L-CDH) fetal flow disturbance results in left cardiac hypoplasia[2–5] which improves after birth, CDH repair[2] and fetal endoscopic tracheal occlusion[6]. The severity of CDH as measured by the lung-to-head ratio (LHR)[7] and presence of liver herniation into the chest is known to be associated with the degree of left heart hypoplasia in-utero[8].

In the fetal circulation, the left heart provides cardiac output to the brain and coronary arteries[9]. Reduction in left ventricular cardiac output (LVCO) has been established in L-CDH[5] however the physiological effects on cerebral blood flow are not well understood. In hypoplastic left heart syndrome (HLHS) diminished cerebral perfusion and oxygen delivery results in an adaptive response with reductions in cerebrovascular resistance as measured by the middle cerebral artery pulsatility index (MCA PI)[10–11]. Neurodevelopmental outcomes in patients with CDH are known to be impaired[12–18]. The etiology is likely multifactorial including genetic factors, postnatal cardiopulmonary instability, and chronic illness related to severity of the clinical course[19–21]. However, given the fetal flow disturbances described in fetuses with L-CDH that may alter cerebral blood flow, it is plausible that impaired cerebral perfusion in utero can influence neurodevelopmental outcomes and cerebral development.

Our aims for this study were to 1) compare cerebrovascular resistance in fetuses with L-CDH and right CDH (R-CDH) to unaffected (control) fetuses; 2) evaluate the correlation between fetal cerebral vascular resistance and LVCO; and 3) describe neurodevelopmental outcomes in this cohort of infant survivors of CDH. We hypothesized that cerebral vascular resistance would be reduced in the setting of L-CDH, secondary to lower LVCO as compared to control fetuses but unchanged in those with R-CDH compared with controls.

PATIENTS AND METHODS

The clinical and sonographic data of fetuses with R- or L-CDH evaluated at the Benioff Children's Hospital Fetal Treatment Center at the University of California San Francisco between 2011-2018 were retrospectively reviewed. This included fetal sonograms and echocardiograms, an integral component of standard clinical management of a fetus with CDH in our center. Exclusion criteria consisted of significant congenital heart disease (CHD) (described below), known chromosomal or genetic abnormalities, and twin gestation. Gestational age-matched singleton fetuses with normal cardiovascular anatomy, normal uteroplacental function and normal extracardiac anatomy were chosen to comprise the unaffected control group.

Sonographic data collected on subjects with CDH included LHR and the presence or absence of liver herniation. LHR is calculated by dividing the area of the unaffected lung by the fetal head circumference[7]. In addition, estimated fetal weight (EFW), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) were also collected. This data was obtained from the sonogram performed within 24 hours of the fetal echocardiogram. All included subjects (CDH and unaffected fetuses) underwent a complete standard of care fetal echocardiogram. This includes multiple tomographic views of the fetal heart according to the AIUM guidelines[22] as well as color Doppler and pulsed-wave spectral Doppler examination of the umbilical cord, venous structures and middle cerebral artery. Studies were performed on Sequoia C512, S2000 or GE E10 ultrasound systems (Siemens, Mountain View, CA, USA and GE Healthcare, Milwaukee, WI, USA). The images were stored digitally in standard DICOM format. Two pediatric cardiologists (K.A.K. and W.J.H.) reviewed the echocardiograms. Vascular resistance, expressed as the pulsatility index, was obtained from the middle cerebral artery using the following equation: MCA PI= (peak systolic velocity-end-diastolic velocity)/time averaged maximum velocity). The MCA PI was transformed to a z-score for gestational age based on published normative data[23]. Similarly, the pulsatility index in the umbilical artery (UA PI) was calculated and a resultant cerebro-placental ratio was determined (MCA PI/UA PI). The cardiac output for each ventricle was calculated using the following equation: cardiac output= heart rate x (velocity time integral x valve area). The combined cardiac output (CCO) was calculated as the sum of the right and left ventricular cardiac output. Measurements of the aortic and pulmonic valve were obtained from a 2D image from inner edge to inner edge of the valve at onset-systole. Aortic and pulmonic velocity time integrals were planimetered and averaged over three cardiac cycles from a spectral Doppler sample taken with an angle <20 degrees to the direction of flow. The percent of CCO from each ventricle was calculated by the ratio of left ventricular output (LVCO/CCO) and right ventricular output (RVCO/CCO) to CCO. To measure inter-reader reliability, a faculty echocardiographer (S.P.) measured the MCA PI on a randomly selected 20% of the subjects and compared them to the original measurements. The intraclass correlation coefficient of the MCA PI was 97.7% (95% CI: 95.9-99.7%).

A subset of survivors underwent neurodevelopmental testing as part of routine clinical care. Patients were administered the Bayley Scales of Infant Development-3rd Edition (BSID-III) by either a licensed psychologist or trained nurse practitioner. The motor, cognitive and language summary scores were collected and analyzed for this study.

Statistical analysis:

Standard descriptive statistics were utilized. Univariate analyses involved comparisons with two-sample Student t-test or linear regression for parametric data and the Mann-Whitney test for non-parametric data. Multivariable analyses were performed using linear regression equations adjusting for relevant variables for continuous outcomes. P-values < 0.05 were considered statistically significant. All analyses were performed with STATA version 14.2 (Stata Statistical Software: Release 14, College Station, TX: Stata Corp LP). The study was approved by the UCSF institutional committee on human research with a waiver of consent.

RESULTS

Between 2011 and 2018, 95 subjects with available data were referred to UCSF for evaluation of CDH (80 L-CDH and 15 R-CDH). The unaffected comparative group was comprised of 27 subjects. Demographics and characteristics of the entire cohort of CDH fetuses are presented in Table 1 prior to applying the exclusion criteria for the current study. Six (7.5%) subjects with L-CDH were excluded for significant CHD consisting of aortic coarctation, right dominant unbalanced complete atrioventricular canal with hypoplastic left ventricle, atrioventricular canal defect, tetralogy of Fallot, tetralogy of Fallot with absent pulmonary valve, double outlet right ventricle with mitral atresia and aortic coarctation with multiple ventricular septal defects. Subjects with CHD (isolated small muscular ventricular septal defect, right aortic arch, and left superior vena cava to coronary sinus) unlikely to cause hemodynamic disturbance in utero were included. Subjects with known genetic abnormalities (n= 11), including trisomy 21, mosaic Turner's syndrome and 22q11.2 deletion syndrome, were excluded. Extracardiac abnormalities confirmed postnatally are listed in Table 1. Those with structural brain anomalies were also excluded from the analysis. Pregnancy outcomes included termination of pregnancy in 25 cases (L-CDH: n= 20, 25%; R-CDH: n= 5, 33.3%) and fetal death in 2 subjects (2.5%) with L-CDH.

After applying the exclusion criteria, 53 subjects with L-CDH and 11 subjects with R-CDH that had available fetal hemodynamic data were analyzed (Table 2). There was no significant difference in the mean gestational age at the time of fetal echocardiogram or estimated fetal weight between CDH and control subjects (Control: 22.8 wks, 95% CI: 21.7-23.9; L-CDH: 24.0 wks, 95% CI: 23.2-24.9, p= 0.09; R-CDH: 22.6 wks, 95% CI: 20.8-24.3, p= 0.8). The mean LHR in the L-CDH group was 1.07 (95% CI: 0.97-1.2) and in the R-CDH group was 0.98 (95% CI: 0.73-1.2). 67.9% (n= 36) of the L-CDH group had the liver herniated into the thorax. When evaluating LV output as a percentage of combined cardiac output (ratio of LVCO/CCO), fetuses with L-CDH had lower values compared with control fetuses (Control= 0.38, 95% CI: 0.33-0.42; L-CDH= 0.32, 95% CI: 0.29-0.35, p= 0.04), while the ratio of RVCO/CCO was higher (Control 0.62, 95% CI: 0.58-0.66; L-CDH= 0.68, 95% CI: 0.65-0.71, p= 0.01). In fetuses with R-CDH, there were no differences when compared to controls (LVCO/CCO: 0.42, 95% CI: 0.34-0.5, p= 0.26; RVCO/CCO: 0.58, 95% CI: 0.50-0.66, p= 0.26). Fetuses with L-CDH had a trend towards a slightly larger BPD as compared to control fetuses (L-CDH: 5.8, 95% CI: 5.6-6.1; Control: 5.4,95% CI: 5.0-5.7, p= 0.05). There was no significant difference in HC when comparing each CDH group to the unaffected group.

The MCA PI z-score was significantly lower in L-CDH (−1.3, 95% CI: −1.6, −1.0) as compared to control fetuses (0.08, 95% CI: −0.5, 0.6; p< 0.001) (Table 3 and Figure 1). In fetuses with R-CDH, the MCA PI z-scores (−0.7, 95% CI: −1.4, −0.01) did not differ from unaffected fetuses (p= 0.14). The UA PI did not differ in the R- or L-CDH group compared with the control group. Consequently, the cerebro-placental ratio (MCA PI/UA PI) was significantly lower in the L-CDH group compared with control fetuses (p= 0.0012). After adjusting for gestational age and estimated fetal weight at the time of the fetal echocardiogram in a multi-variable model, we found minimal impact of the timing of fetal echocardiogram and size of the fetus on the difference in MCA PI z-score between L-CDH and control groups (−1.3, 95% CI: −1.8, −0.7, p< 0.001). There was a significant association between the percentage of LV cardiac output (LVCO/CCO) and the MCA PI z-score, in an analysis including all fetuses. For every 5% increase in the percentage of LV cardiac output the MCA PI z-score increased by 0.22, 95% CI: 0.05–0.39, p= 0.01 (Figure 2). There was no correlation between LHR and MCA PI z-score (r= −0.1, p= 0.35). In addition, the presence of liver in the thorax was not associated with MCA PI z-score among the L-CDH subjects (Liver herniated: −1.2, 95% CI: −1.5, −0.87; Liver not herniated: −1.5, 95% CI: −2.4, −0.8, p= 0.3)

A subset of surviving patients had neurodevelopmental outcome testing with the BSID-III in early (n= 20) and late infancy (n= 15) (Table 4). At both time points, the mean cognitive and language scores were within normal limits. A small number of subjects (n= 5) had abnormal motor scores at any time point (< 85).

DISCUSSION

Our study demonstrates that fetuses with L-CDH have significantly lower cerebral vascular resistance compared with control fetuses. The percentage of LV cardiac output in L-CDH fetuses was low and directly correlated with the MCA PI z-score. Our findings suggest that diminished LVCO may affect cerebral vascular resistance as a compensatory mechanism.

Our findings highlight several important physiologic considerations. First, similar to prior studies[2–5], our study reports lower LVCO compromising 32% of the total cardiac output compared to 38% in unaffected fetuses. In contrast, LVCO in R-CDH was similar to control fetuses, though the sample size was small. This finding diverges slightly from those of Byrne et al[5], possibly due to less severe cases being included in our analysis. Diminished LVCO in L-CDH may be due to a mass effect with varying physiologic mechanisms proposed including decreased pulmonary venous return and/or diminished right-to-left foramen ovale flow as a result of altered geometry of the ductus venosus [3–5,24–27] Our findings support the latter as the right ventricular cardiac output as a percentage of the total cardiac output was significantly higher in the L-CDH group (68%) as compared to the control fetuses (62%).

Second, cerebral vascular resistance was significantly lower in the L-CDH group compared with control fetuses and may be associated with diminished antegrade flow to the cerebral circulation. Other studies have demonstrated decreased MCA peak systolic velocity in L-CDH[28], but found no difference in MCA PI when comparing to published normative data. Our study differed in that comparisons were made to control fetuses in our center with

similar measurement techniques. Our findings suggest a compensatory mechanism to provide adequate cerebral blood flow to the fetal brain which has been reported in other disease states, though the etiologies likely differ. Fetuses with placental insufficiency and growth restriction exhibit a chronic hypoxic state and diminished cerebral vascular resistance, which may represent a protective mechanism against postnatal neurologic injury[29–30]. This compensation may be inadequate as these patients born prematurely have neurobehavioral abnormalities later in life[31]. Similarly, fetuses with HLHS also exhibit lower cerebral vascular resistance[10–11], thought to be secondary to decreased perfusion and oxygen delivery to the brain[32]. A large multi-center study demonstrated that lower cerebral vascular resistance in HLHS fetuses was associated with better neurodevelopmental outcomes at 14 months of age[33]. Given the absence of structural heart disease among the L-CDH subjects in this series, our findings provide a model of diminished antegrade perfusion to the fetal brain presumably in the absence of significant hypoxia, though changes in fetal streaming patterns cannot be excluded. Our results suggest that isolated diminished cerebral perfusion potentially influences local vascular properties. Since various factors can affect the MCA PI (perfusion, oxygen, carbon dioxide and local metabolic properties)[34–37], our study did not establish causality between low left ventricular output and MCA PI, but rather demonstrates an association.

The R-CDH group did not have significantly different MCA PI z-scores compared with the control fetuses, potentially secondary to having a relatively normal cardiac output from the left ventricle as a percentage of the combined cardiac output. However, there was a slight trend towards a lower MCA PI z-score in this group. This observation may be secondary to a different physiologic mechanism than the L-CDH group. Changes in the inferior vena cava and ductus venosus geometry in CDH, which may be severe in cases of R-CDH with liver herniation,[25] may potentially lead to alterations in streaming patterns with less oxygenated blood being directed towards the foramen ovale and left heart. Studies utilizing fetal cardiac MRI assessing fetal brain flow and oximetry in CDH would provide clarity to this question[32].

In the recent era, moderate-to-severe L-CDH cases are considered for in-utero intervention with fetal endoscopic tracheal occlusion (FETO), which has been shown to increase perinatal survival, reduce extracorporeal membrane oxygenation (ECMO)[38–39] and decrease pulmonary hypertension postnatally[40]. Fetal left sided cardiac structures and LVCO show positive increases after FETO[6]. Thus, it is intriguing to speculate if FETO may improve antegrade cerebral blood flow and potentially modify neurodevelopmental outcomes. The patients in our cohort did not undergo FETO, therefore we were unable to test the influence of this procedure on the MCA PI.

Measures of brain growth in L-CDH subjects were similar to slightly larger compared to control fetuses (BPD and HC) as has been previously shown[28]. In addition, among the subset of CDH patients that underwent neurodevelopmental testing in infancy, scores were similar to what would be expected in the general population (within one standard deviation). These descriptive findings slightly diverge from larger studies on short- and long-term outcomes in CDH survivors[41–42] which demonstrate that higher risk patients (i.e. ECMO, persistent ventilatory support and feeding dysfunction) have evidence of

neurodevelopmental deficits. Our study was not powered to address neurodevelopmental outcomes given that other factors may contribute to the ultimate outcome such as comorbidities, gestational age at delivery, acute cardiopulmonary instability and chronic illness[12–18]. Secondly, it is possible that the subset of subjects with neurodevelopmental data represents a skewed sample of the highest functioning survivors. Given the small sample size of patients with neurodevelopmental outcome data in our study, we were unable to formally test the relationship between cerebral vascular resistance and neurodevelopmental outcome accounting for all potential confounders, though our findings may represent a fetal compensatory mechanism in response to diminished antegrade cerebral blood flow.

The strengths of our study include the relatively large sample size of subjects with L-CDH and an unaffected comparative group from our institution with detailed fetal echocardiograms. However, our study is limited by its retrospective nature, the small number of patients with neurodevelopmental outcome data and the lack of other objective data on fetal brain development that would be obtained on fetal or neonatal brain magnetic resonance imaging.

In conclusion, we found that fetuses with L-CDH have lower LVCO and this correlated with lower cerebral vascular resistance, indicating a possible compensatory mechanism in fetuses with moderate-to-severe L-CDH. Our study provides a model of the effects of isolated diminished antegrade cerebral blood flow on cerebral vascular resistance. Larger studies with prospective collection of neurodevelopmental testing are needed to understand the implications of these findings to further aid in adjusting therapeutic strategies, providing counseling and managing affected patients.

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REFERENCES

1. Baumgart S, Paul JJ, Huhta JC, Katz AL, Paul KE, Spettell C, Spitzer AR. Cardiac malposition, redistribution of fetal cardiac output, and left heart hypoplasia reduce survival in neonates with congenital diaphragmatic hernia requiring extra corporeal membrane oxygenation. J Pediatr. 1998; 133(1): 57–62. [PubMed: 9672511]
2. Vogel M, McElhinney DB, Marcus E, Morash D, Jennings RW, Tworetzky W. Significance and outcome of left heart hypoplasia in fetal congenital diaphragmatic hernia. Ultrasound Obstet Gynecol. 2010; 35(3): 310–317. [PubMed: 20143332]
3. Siebert JR, Haas JE, Beckwith JB. Left ventricular hypoplasia in congenital diaphragmatic hernia. J Pediatr Surg. 1984; 19(5): 567–571. [PubMed: 6502429]
4. VanderWall KJ, Kohl T, Adzick NS, Silverman NH, Hoffman JI, Harrison MR. Fetal diaphragmatic hernia: echocardiography and clinical outcome. J Pediatr Surg. 1997; 32(2): 223–225. [PubMed: 9044126]
5. Byrne FA, Keller RL, Meadows J, Miniati D, Brook MM, Silverman NH, Moon-Grady AJ. Severe left diaphragmatic hernia limits size of fetal left heart more than does right diaphragmatic hernia. Ultrasound Obstet Gynecol. 2015; 46(6): 688–694. [PubMed: 25597867]
6. Rocha LA, Byrne FA, Keller RL, Miniati D, Brook MM, Silverman NH, Moon-Grady AJ. Left heart structures in human neonates with congenital diaphragmatic hernia and the effect of fetal endoscopic tracheal occlusion. Fetal Diagn Ther. 2014; 35(1): 36–43. [PubMed: 24356206]

7. Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. J Pediatr Surg. 1996; 31(1): 148–152. [PubMed: 8632269]
8. Kailin JA, Dhillon GS, Maskatia SA, Cass DL, Shamshirsaz AA, Mehollin-Ray AR, Cassady CI, Ayres NA, Wang Y, Belfort MA, Olutoye OO, Ruano R. Fetal left-sided cardiac structural dimensions in left-sided congenital diaphragmatic herniaassociation with severity and impact on postnatal outcomes. Prenat Diagn. 2017; 37(5): 502–509. [PubMed: 28370263]
9. Rudolph AM. Congenital Diseases of the Heart: Clinical-Physiological Considerations. 3rd ed. Chichester, UK: Wiley-Blackwell, 2009.
10. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. Ultrasound Obstet Gynecol. 2005; 25(1): 32–36. [PubMed: 15593334]
11. Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, Cetta F, Falkensammer CB, Huhta JC, Kleinman CS. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. Pediatr Cardiol. 2003; 24(5): 436–443. [PubMed: 14627309]
12. Van Meurs KP, Robbins ST, Reed VL, Karr SS, Wagner AE, Glass P, Anderson KD, Short BL. Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. J Pediatr. 1993; 122(6): 893–899. [PubMed: 8501565]
13. Nobuhara KK, Lund DP, Mitchell J, Kharasch V, Wilson JM. Long-term outlook for survivors of congenital diaphragmatic hernia. Clin Perinatol. 1996; 23(4): 873–887. [PubMed: 8982576]
14. Friedman S, Chen C, Chapman JS, Jeruss S, Terrin N, Tighiouart H, Parsons SK, Wilson JM. Neurodevelopmental outcomes of congenital diaphragmatic hernia survivors followed in a multidisciplinary clinic at ages 1 and 3. J Pediatr Surg. 2008; 43(6): 1035–1043. [PubMed: 18558179]
15. Jakobson LS, Frisk V, Trachsel D, O'Brien K. Visual and fine-motor outcomes in adolescent survivors of high-risk congenital diaphragmatic hernia who did not receive extracorporeal membrane oxygenation. J Perinatol 2009; 29(9): 630–636. [PubMed: 19461591]
16. Frisk V, Jakobson LS, Unger S, Trachsel D, O'Brien K. Long-term neurodevelopmental outcomes of congenital diaphragmatic hernia survivors not treated with extracorporeal membrane oxygenation. J Pediatr Surg. 2011; 46(7): 1309–1318. [PubMed: 21763827]
17. Tureczek I, Caflish J, Moehrlen U, Natalucci G, Bernet V, Latal B. Long-term motor and cognitive outcome in children with congenital diaphragmatic hernia. Acta Pediatr. 2012; 101(5): 507–512.
18. Leeuwen L, Schiller RM, Rietman AB, van Rosmalen J, Wildschut ED, Houmes RJM, Tibboel D, IJsselstijn H. Risk factors of impaired neuropsychologic outcome in school-aged survivors of neonatal critical illness. Crit Car Med. 2018; 46(3): 401–410.
19. Stolar CJ, Crisafi MA, Driscoll YT. Neurocognitive outcome for neonates treated with extracorporeal membrane oxygenation: are infants with congenital diaphragmatic hernia different? J Pediatr Surg. 1995; 30(2): 366–371. [PubMed: 7537811]
20. Danzer E, Kim SS. Neurodevelopmental outcome in congenital diaphragmatic hernia: evaluation, predictors and outcome. World J Clin Pediatr. 2014; 3(3): 30–36. [PubMed: 25254182]
21. Danzer E, Hoffman C, D'Agostino JA, Gerdes M, Bernbaum J, Antiel RM, Rintoul NE, Herkert LM, Flake AW, Adzick NS, Hedrick HL. Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia. J Pediatr Surg. 2017; 52(3): 437–443. [PubMed: 27622588]
22. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of fetal echocardiography. J Ultrasound Med. 2013; 32(6): 1067–1082. [PubMed: 23716531]
23. Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol. 2007; 30(3): 287–296. [PubMed: 17721916]
24. Allan LD, Irish MS, Glick PL. The fetal heart in diaphragmatic hernia. Clin Perinatol. 1996; 23(4): 795–812. [PubMed: 8982572]
25. Stressig R, Fimmers R, Eising K, Gembruch U, Kohl T. Preferential streaming of the ductus venosus and inferior caval vein towards the right heart is associated with left heart underdevelopment in human fetuses with left-sided diaphragmatic hernia. Heart. 2010; 96(19): 1564–1568. [PubMed: 20702536]

26. Schwartz SM, Vermilion RP, Hirschl RB. Evaluation of left ventricular mass in children with left-sided congenital diaphragmatic hernia. J Pediatr. 1994; 125(3): 447–451 [PubMed: 8071756]
27. Crawford DC, Drake DP, Kwaitkowski D, Chapman MG, Allan LD. Prenatal diagnosis of reversible cardiac hypoplasia associated with congenital diaphragmatic hernia: implications for postnatal management. J Clin Ultrasound. 1986; 14(9): 718–721. [PubMed: 3098794]
28. Van Mieghem T, Sandaite I, Michielsen K, Gucciardo L, Done E, Dekoninck P, Claus F, Deprest J. Fetal cerebral blood flow velocities in congenital diaphragmatic hernia. Ultrasound Obstet Gynecol. 2010; 36(4): 452–457. [PubMed: 20521239]
29. Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The “brain sparing” effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol. 1993; 169(1): 169–175. [PubMed: 8333447]
30. Scherjon SA, Oosting H, Smolders-DeHaas H, Zondervan HA, Kok JH. Neurodevelopmental outcome at three years of age after fetal ‘brain sparing’. Early Hum Dev. 1998; 52(1): 67–69. [PubMed: 9758249]
31. Figueras F, Cruz-Martinez R, Sanz-Cortes M, Arranz A, Illa M, Botet F, Costas-Moragas C, Gratacos E. Neurobehavioral outcomes in preterm, growth-restricted infants with and without prenatal advanced signs of brain-sparing. Ultrasound Obstet Gynecol. 2011; 38(3): 288–294. [PubMed: 21557369]
32. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015; 131(15): 1313–1323. [PubMed: 25762062]
33. Williams IA, Fifer C, Jaeggi E, Levine JC, Michelfelder EC, Szwast AL. The association of fetal cerebrovascular resistance with early neurodevelopment in single ventricle congenital heart disease. Am Heart J. 2013; 165(4): 544–550.e1. [PubMed: 23537971]
34. Smirl JD, Tzeng YC, Monteleone BJ, Ainslie PN. Influence of cerebrovascular resistance on the dynamic relationship between blood pressure and cerebral blood flow in humans. J Appl Physiol. 2014; 116(12): 1614–1622. [PubMed: 24744385]
35. Phillips AA, Chan FHN, Zheng MMZ, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: physiology, methodological advances and clinical implications. J Cereb Blood Flow Metab. 2015; 36(4): 647–664. [PubMed: 26661243]
36. Duffin J, Sobczyk O, McKetton L, Crawley A, Poublanc J, Venkatraghavan L, Sam K, Mutch WA, Mikulis D, Fisher JA. Cerebrovascular resistance: the basis of cerebrovascular reactivity. Front Neurosci. 2018; 12: 409. [PubMed: 29973862]
37. Masamoto K, Tanishita K. Oxygen transport in brain tissue. J Biomech Eng. 2009; 131(7): 074002. [PubMed: 19640134]
38. Belfort MA, Olutoye OO, Cass DL., Olutoye OA, Cassady CI, Mehollin-Ray AR, Shamshirsaz AA, Cruz SM, Lee TC, Mann DG, Espinoza J, Welty SE, Fernandes CJ, Ruano RR. Feasibility and outcomes of fetoscopic tracheal occlusion for severe left diaphragmatic hernia. Obstet Gynecol 2017; 129(1): 20–29. [PubMed: 27926636]
39. Jani JC, Nicolaides KH, Gratacós E, Valencia CM, Doné E, Martinez JM, Gucciardo L, Cruz R, Deprest JA. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. Ultrasound Obstet Gynecol. 2009; 34(3): 304–310. [PubMed: 19658113]
40. Style CC, Olutoye OO, Belfort MA, Ayres NA, Cruz SM, Lau PE, Shamshirsaz AA, Lee TC, Olutoye OA, Fernandes CJ, Sanz-Cortes M, Keswani SG, Espinoza J. Fetal endoscopic tracheal occlusion reduces pulmonary hypertension in severe congenital diaphragmatic hernia. Ultrasound Obstet Gynecol. Epub 2019 Jan 14. doi: 10.1002/uog.20216.
41. Wynn J, Aspelund G, Zygmunt A, Stolar CJ, Mychaliska G, Butcher J, Lim FY, Gratton T, Potoka D, Brennan K, Azarow K, Jackson B, Needelman H, Cromblehome T, Zhang Y, Duong J, Arkovitz MS, Chung WK, Farkouh C. Developmental outcomes of children with congenital diaphragmatic hernia: a multicenter prospective study. J Pediatr Surg. 2013; 48(10): 1995–2004. [PubMed: 24094947]

42. Church JT, Mon R, Wright T, Coughlin MA, Ladino-Torres M, Tapley C, Bowen H, Matusko N, Mychaliska GB. Neurodevelopmental outcomes in CDH survivors: A single institution's experience. J Pediatr Surg. 2018; 53(6): 1087–1091. [PubMed: 29580786]

What are the novel findings of this work?

Left sided cardiac output is diminished in left congenital diaphragmatic hernia. Our study shows that these fetuses also exhibit decreased cerebral vascular resistance in the setting of diminished left cardiac output.

What are the clinical implications of this work?

Survivors of congenital diaphragmatic hernia possess neurodevelopmental delays, which are multifactorial in origin. Altered cerebral blood flow in-utero may contribute to neurodevelopmental outcomes in this patient population.

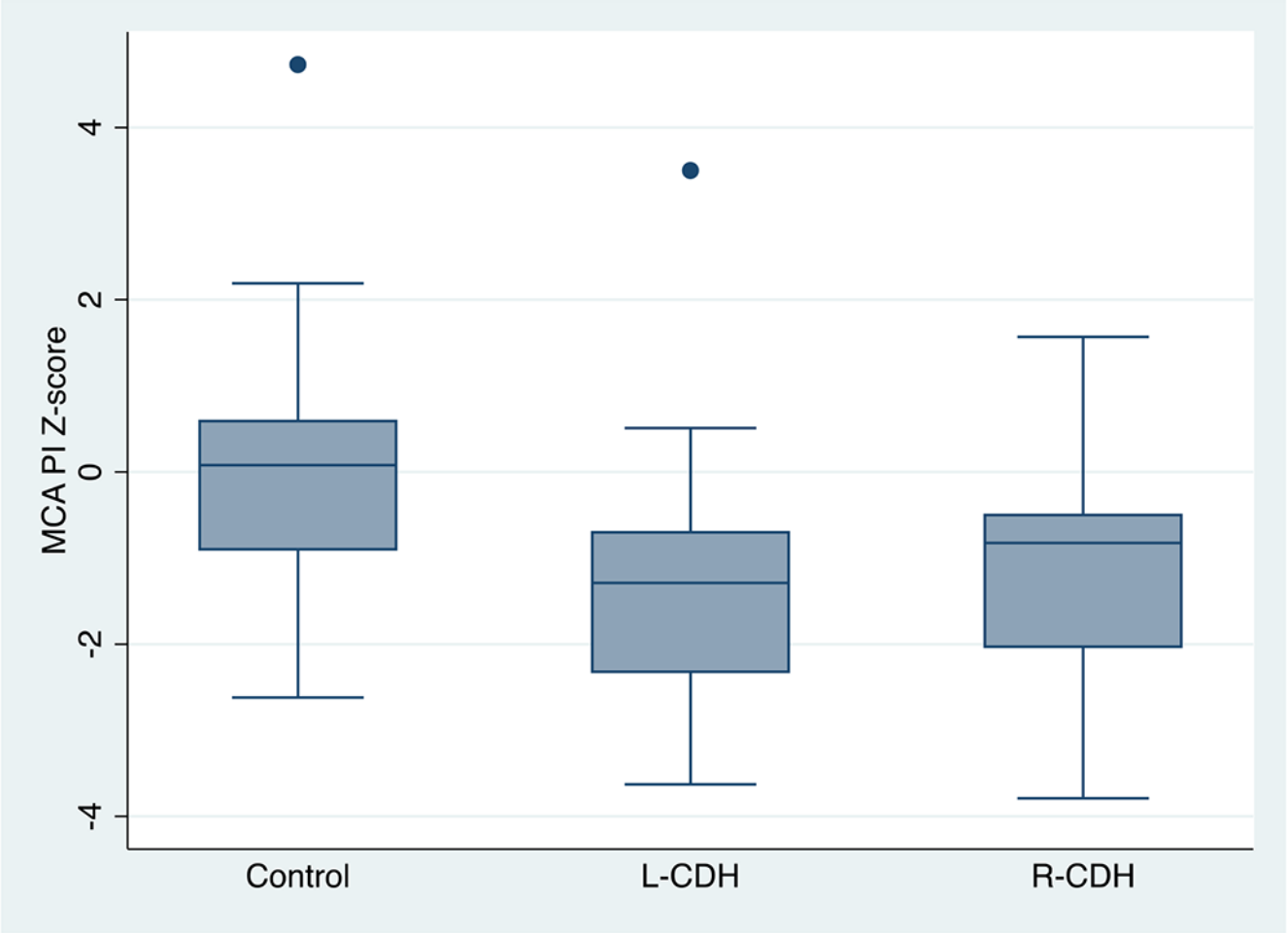

Figure 1.
Box and whisker plots for MCA PI z scores in control, L-CDH and R-CDH groups.

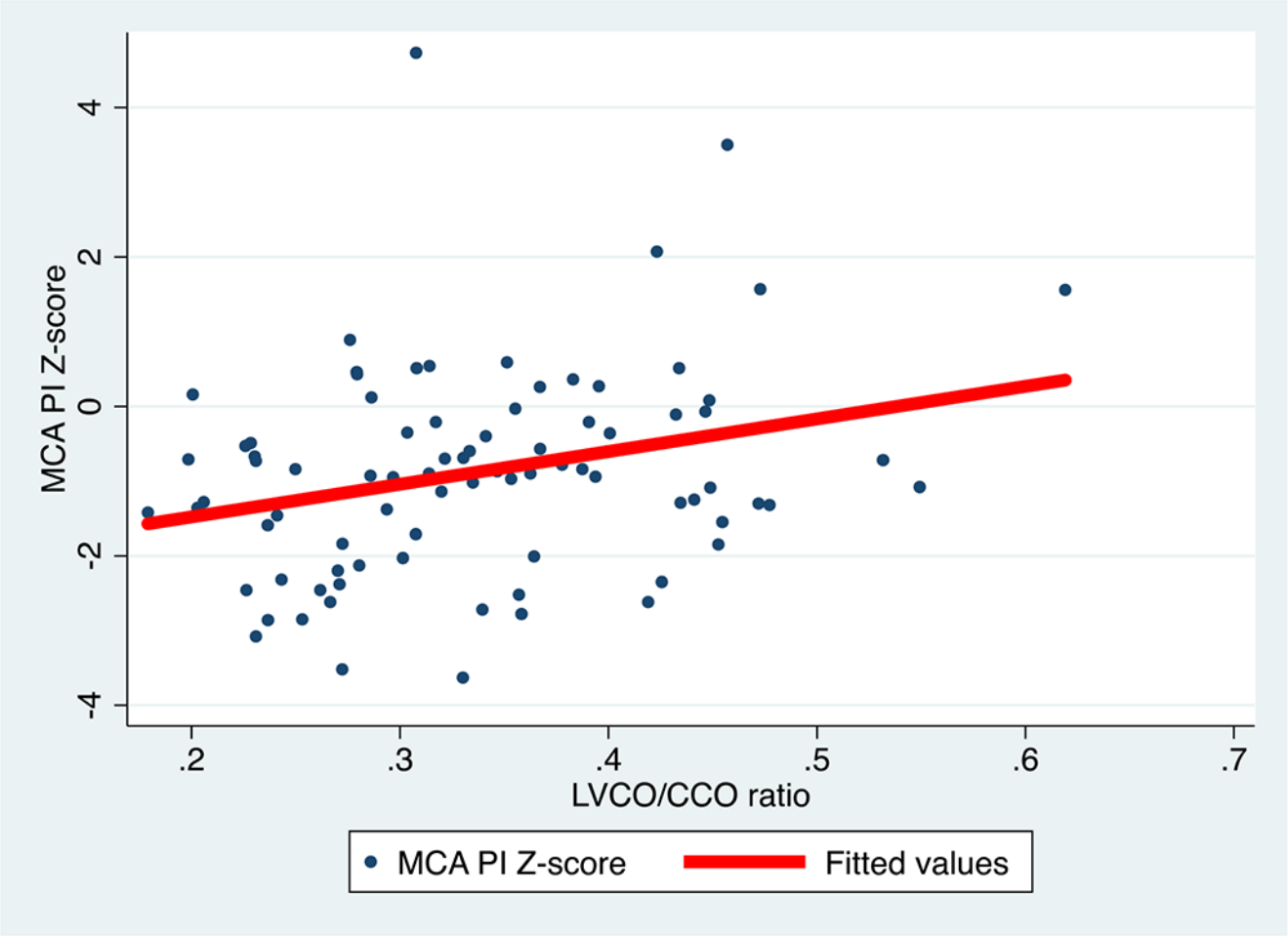

Figure 2.
Scatterplot and linear fit of the ratio of left ventricular cardiac output (LVCO) to combined cardiac output (CCO) vs MCA PI z-score for all subjects.

Table 1.

Demographics of congenital diaphragmatic hernia subjects.

	L-CDH (n= 80)	R-CDH (n= 15)
Other Anomalies		
2 vessel cord, N(%)	7 (8.7%)	0
Renal anomalies, N (%)	5 (6.2%)	0
GI anomalies, N (%)	6 (7.5%)	1 (6.7%)
Brain anomalies, N (%)	4 (5%)	0
Other lung anomalies, N (%)	5 (6.2%)	1 (6.7%)
CHD significant*, N (%)	6 (7.5%)	0
Genetic Abnormality, N (%)	10 (12.5%)	1 (6.7%)
Perinatal Outcome		
Termination of pregnancy, N (%)	20 (25%)	5 (33.3%)
IUFD, N (%)	2 (2.5%)	0
Gestation age at birth, weeks (mean, 95% CI)	38.6 (38.1-39.1)	36.8 (34.2-39.4)
CDH characteristics		
LHR, mean (95% CI)	1.05 (0.96-1.13)	1 (0.79-1.20)
Liver herniated into thorax N (%)	55 (67.1%)	15 (100%)

Abbreviations: L-CDH, left congenital diaphragmatic hernia; R-CDH, right congenital diaphragmatic hernia; CHD, congenital heart disease; IUFD, intrauterine fetal demise; LHR, lung-to-head ratio.

*Significant CHD included conotruncal defect, atrioventricular canal defects, severe left sided obstruction, and multiple or large ventricular septal defect.

Table 2.

Hemodynamics and baseline biometry in CDH and control subjects with available data after excluding those with significant congenital heart disease, chromosomal/genetic abnormalities and structural brain anomalies.

	Control (n= 27)	L-CDH (n= 53)	P-value*	R-CDH (n= 11)	p-value+
GA at fetal echo, mean (95% CI)	22.8 (21.7-23.9)	24.0 (23.2-24.9)	0.09	22.6 (20.8-24.3)	0.8
EFW (kg), mean (95% CI)	0.59 (0.40-0.78)	0.72 (0.62-0.81)	0.22	0.65 (0.42-0.87)	0.69
LHR (mean, 95% CI)		1.07 (0.97-1.2)	--	0.98 (0.73-1.2)	--
Liver herniated into thorax (N, %)		36 (67.9%)		11 (100%)	
LVCO (cc/min) Mean, 95% CI	93.5 (68.2-118)	95.6 (66.7-124.1)	0.9	97.1 (52.7-141)	0.87
RVCO (cc/min) Mean, 95% CI	148.4 (114.7-182.0)	186.3 (160.9-211.7)	0.08	126.5 (97.3-155.6)	0.4
CCO (cc/min) Mean, 95% CI	241.9 (186.1-297.7)	283.6 (239.4-327.8)	0.19	225.2 (150.4-300)	0.7
CCOi (cc/min/kg) Mean, 95% CI	364.2 (308.4-420)	414.5 (378.2-450.0)	0.17	366.5 (240.3-492.7)	0.9
LVCO/CCO Mean, 95% CI	0.38 (0.33-0.42)	0.32 (0.29-0.35)	0.04	0.42 (0.34-0.50)	0.26
RVCO/CCO Mean, 95% CI	0.62 (0.58-0.66)	0.68 (0.65-0.71)	0.01	0.58 (0.50-0.66)	0.26
Head circumference (cm) Mean, 95% CI	20.5 (19.2-21.8)	22.0 (21.0-22.9)	0.08	20.7 (19.2-22.5)	0.81
Biparietal diameter (cm) Mean, 95% CI	5.4 (5.0-5.7)	5.8 (5.6-6.1)	0.05	5.5 (5.1-6.0)	0.54

Abbreviations: L-CDH, left congenital diaphragmatic hernia; R-CDH, right congenital diaphragmatic hernia; GA, gestational age; LHR, lung-to-head ratio; LVCO, left ventricular cardiac output; RVCO, right ventricular cardiac output; CCO, combined cardiac output; CCOi, combined cardiac output indexed to fetal weight

* p-value represents comparison between L-CDH and control fetuses using a two-sample t-test

+ p-value represents comparison between R-CDH and control fetuses using a two-sample t-test

Table 3.

Fetal middle cerebral artery and umbilical artery pulsatility indices in the three study groups.

	Control (n= 27)	L-CDH (n= 53)	P-value*	R-CDH (n= 11)	p-value+
MCA PI z-score Mean, 95% CI	0.08 (−0.5, 0.6)	−1.3 (−1.7, −1.0)	<0.001	−0.70 (−1.4,−0.01)	0.14
UA PI Mean, 95% CI	1.2 (1.1-1.3)	1.2 (1.1-1.2)	0.85	1.2 (1.0-1.2)	0.8
MCA/UA PI Mean, 95% CI	1.6 (1.4-1.8)	1.3 (1.2-1.3)	0.0012	1.3 (1.1-1.4)	0.08

Abbreviations: L-CDH, left congenital diaphragmatic hernia; R-CDH, right congenital diaphragmatic hernia; MCA PI, middle cerebral artery pulsatility index; UA PI, umbilical artery pulsatility index

* p-value represents comparison between L-CDH and control fetuses using a two-sample t-test

+ p-value represents comparison between R-CDH and control fetuses using a two-sample t-test

Table 4.

Neurodevelopmental outcomes for a subset of CDH subjects that presented for evaluation.

	Infancy (n= 20)	**Early Childhood (n= 15)**
Age at evaluation (months, 95% CI)	15.5 (13.8-17.2)	31.5 (29.0-34.1)
BSID-III		
Cognition (mean, 95% CI)	100.8 (94.6-107.1)	100.3 (94.5-106.2)
Language (mean, 95% CI)	96.4 (89.5-103.4)	95.7 (89.4-102.0)
Motor (mean, 95% CI)	92.4 (85.2-99.6)	95.7 (87.4-104.1)

Abbreviations: BSID-III, Bayley Scales of Infant Development, 3rd edition