Session 5: Pathophysiological Phenotypes
Chairs: Florian Kipfmueller and Co-Chair

28th April 11.00 – 13.00

26 Impact of Early Echocardiographic Characteristics on Survival and Extracorporeal Life Support Utilization in Neonates with Congenital Diaphragmatic Hernia

Caroline Yeon-Kyeong Noh[1], Shazia Bhombal[1], Valerie Chock[1], Enrico Danzer[2], Neil Patel[3], Alex Dahlen[1], Matthew Harting[4], Kevin Lally[4], Ashley Ebanks[4], Krisa Van Meurs[1]
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37 Ductus arteriosus flow pattern and outcome prediction in CDH neonates.

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38 Left ventricular hypoplasia and ventricular disproportion in neonates with congenital diaphragmatic hernia

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47 Pathophysiological phenotypes in CDH: frequency and relationship to disease severity

Dr Abhijit Bhattacharya[1], Dr Claudia Massolo[2], Dr Sandy Kirolos[1], Dr Florian Kipfmueller[3], Dr Emily Stenhouse[1], Dr Marie Anne Ledingham[4], Mr Carl Davis[1], Dr Neil Patel[1]
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121 Clinical and Cellular Sexual Dimorphism in Congenital Diaphragmatic Hernia

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Impact of Early Echocardiographic Characteristics on Survival and Extracorporeal Life Support Utilization in Neonates with Congenital Diaphragmatic Hernia

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[Background] Detailed echocardiographic characteristics in CDH infants and the associations between these characteristics and outcomes, particularly how they differ by defect side and size, are unknown.
[Methods] This is a retrospective study of Congenital Diaphragmatic Hernia Study Group Registry data collected in 2015-2020. Early echocardiographic characteristics from the first study within 2 days of life prior to surgical interventions (ECLS or repair) including atrial and ductal shunt directions, severity of pulmonary hypertension, and ventricular sizes and functions were analyzed by defect side and size. Mortality and ECLS use were the outcomes. Multivariate logistic regression models were used.
[Results] A total of 1897 infants with 1630 (86%) L-CDH and 267 (14%) R-CDH were included in the final analysis. Echocardiographic characteristics differed by defect side and size. There were more left-to-right (L-to-R) atrial shunts in L-CDH and more bidirectional or right-to-left (R-to-L) atrial shunts in R-CDH, independent of defect size. Left ventricular (LV) hypoplasia was seen more in L-CDH, especially with larger defects. Severe pulmonary hypertension, right-to-left (R-to-L) shunts, LV hypoplasia, right ventricular (RV) dilation, LV dysfunction, RV dysfunction, and biventricular dysfunction were more common in larger defects (p-for-trend <.001). Ductal R-to-L shunt, atrial bidirectional or R-to-L shunt, LV hypoplasia, and biventricular dysfunction were consistently associated with increased mortality across all models (Figure 1). Similarly, bidirectional atrial shunt and biventricular dysfunction were associated with ECLS use. The associations remained significant even after adjustment for defect size, liver position, and repair method.
[Conclusions] Echocardiographic characteristics present in the first 2 days of life differ by defect side and size. Specific characteristics from the early postnatal echocardiogram are predictive of outcomes. Early recognition of echocardiographic findings associated with adverse outcomes is recommended to implement therapies that may improve outcomes.

Images

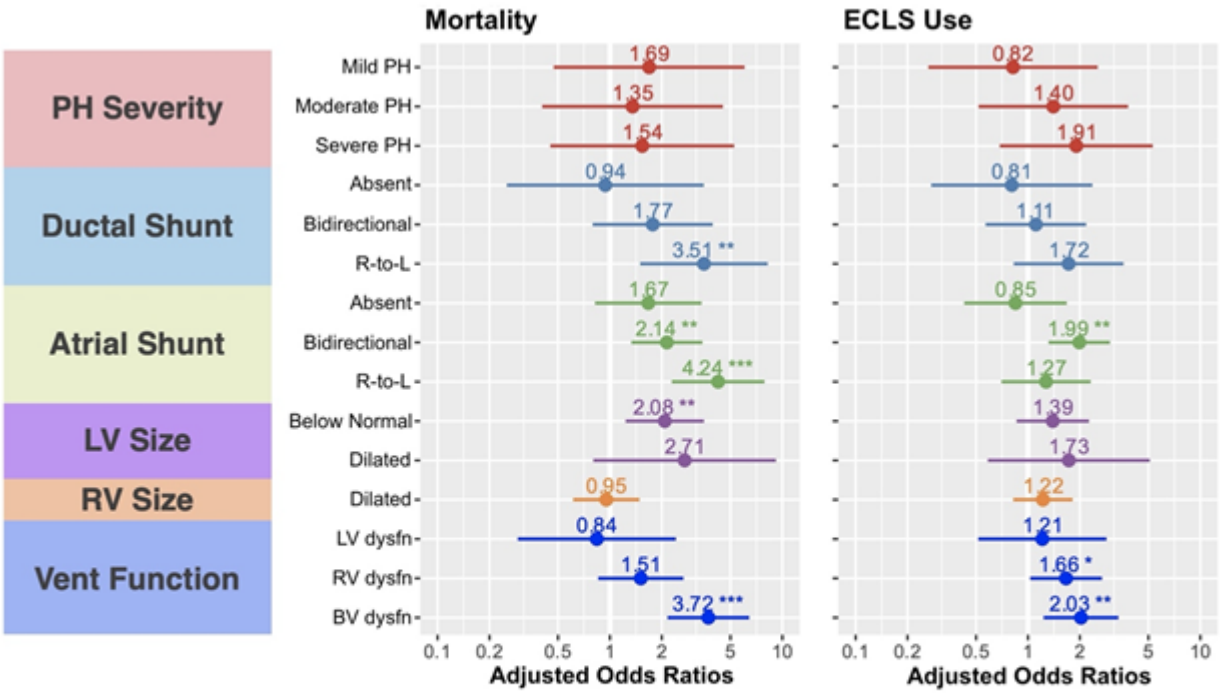

Figure 1. The impact of early echocardiographic characteristics on death and ECLS use based on multivariate regression models. Normal pulmonary arterial pressure, L-to-R shunt, and normal size and function were set as references. Values are presented as 'adjusted OR [95% CI]'. (***, $p < .001$; **, $p < .01$; *, $p < .05$)
(BV, biventricular; dysfn, dysfunction; PH, pulmonary hypertension; vent, ventricular)

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Ductus arteriosus flow pattern and outcome prediction in CDH neonates.

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Background: Pulmonary hypertension (PH) is a major contributor to poor outcome in congenital diaphragmatic hernia (CDH). Early PH assessment is important and PDA flow is routinely obtained during echo assessment. Bidirectional shunting is seen most often but its association with outcome is unclear.

Methods: 139 CDH patients were enrolled in the study. Echocardiography was performed within the first 24 hours of life. PDA flow pattern was quantified by the duration (time) and the velocity time integral (VTI) of left-to-right (LR) shunt and right-to-left (RL) shunt. A timeRL >33% of the cardiac cycle (timeLR+timeRL) and a VTILR/VTIRL <1.0 were defined as abnormal flow pattern. Primary outcome was the need for ECLS or mortality within 48 hours (ECLS/early death). Secondary outcome was death. Patients were allocated according to normal (group 1) or abnormal VTILR/VTIRL (group2).

Results: Overall, 72 patients (51.8%) had a VTILR/VTIRL <1.0, and 73 (52.5%) a timeRL >33%. In 59 patients (42.4%) both indices were abnormal. The baseline characteristics according to group allocation are presented in table 1. The mortality was 19.4% (n=27) and ECLS/early death occurred in 37.4% (n=52). A VTILR/VTIRL <1.0 had the highest diagnostic accuracy with a sensitivity of 82.7%, a specificity of 66.7%, negative predictive value (NPV) of 86.6%, and positive predictive value (PPV) of 59.7% to predict ECLS/early death, and a sensitivity of 77.8%, and a specificity of 54.5% to predict death (NPV 91.0%; PPV 29.2%). Patients with a VTILR/VTIRL <1.0 had a relative risk of 4.5 and 3.3 for ECLS/early death and death, respectively. VTILR/VTIRL values correlated significantly with PH severity (r= -0.516, p<0.001).

Conclusion: Abnormal PDA flow pattern is common during the early transitional phase in CDH neonates. VTILR/VTIRL <1.0 is a valuable threshold to identify low-risk patients. For improved risk assessment, other parameters should be combined with PDA flow assessment.

Images

Variable	Group 1 $VTI_{LR}/VTI_{RL} \geq 1.0$ (n=67)	Group 2 $VTI_{LR}/VTI_{RL} < 1.0$ (n=72)	p-value
Sex, male	35 (52.2)	45 (62.5)	0.234
Gestational age, weeks	38.1 [37.0-39.1]	37.9 [36.5-38.4]	0.140
Birth weight, kg	3.0 [2.5-3.4]	2.9 [2.5-3.3]	0.307
Prenatal diagnosis	61 (91.0)	68 (94.4)	0.522
Left-Sided CDH	62 (92.5)	62 (86.1)	0.279
o/e LHR	42 [37-50]	35 [30-43]	**0.002**
Liver-up CDH	23 (34.3)	41 (56.9)	**0.010**
FETO	6 (9.0)	12 (16.7)	0.212
Age at echo assessment, hours	4.1 [2.1-9.5]	3.1 [1.7-8.1]	0.287
ECLS	9 (13.4)	37 (51.4)	**<0.001**
ECLS/early death	9 (13.4)	43 (59.7)	**<0.001**
Mortality	6 (9.0)	21 (29.2)	**0.003**
Age at ECLS start, hours	19.2 [11.5-34.1]	12.3 [7.6-20.6]	0.154
ECLS duration, days	5.2 [3.4-29.8]	6.3 [3.8-14.2]	1.0
Time echo-to-ECLS, hours	9.1 [6.6-29.9]	8.2 [3.7-16.5]	0.298
Defect Size			**<0.001**
A	9 (14.1)	1 (1.5)	
B	27 (42.2)	11 (16.9)	
C	21 (32.8)	25 (38.5)	
D	4 (6.3)	18 827.7)	
N/R	3 (4.7)	10 (15.4)	
PH			**<0.001**
Mild/No	30 (44.8)	8 (11.1)	
Moderate	28 (41.8)	28 (38.9)	
Severe	9 (13.4)	36 (50.0)	
Cardiac dysfunction			
Right	20 (29.9)	25 (34.7)	0.584
Left	1 (1.5)	2 (2.8)	1.0
Biventricular	10 (14.9)	30 (41.7)	**<0.001**

Data described as absolute number n (%), or median [IQR].

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Left ventricular hypoplasia and ventricular disproportion in neonates with congenital diaphragmatic hernia

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Background

Pulmonary hypertension, cardiac dysfunction, and left ventricular (LV) hypoplasia are established prognostic factors in CDH patients. Extensive studies on ventricular disproportion are lacking.

The primary aim of this study was to evaluate the association of ventricular disproportion described as right ventricular end-diastolic diameter to LV end diastolic diameter ratio (RVD/LVD) with adverse outcomes.

Methods

Echo studies of CDH newborns admitted to NICU at University Children´s Hospital of Bonn between January 2011 and March 2021 obtained within the first 6 hours of life were reviewed. Primary and secondary clinical endpoint were mortality and ECMO or early death within first 48 hours of life. RVD/LVD were obtained from an apical 4-chamber view. Additionally, RVD/LVD was calculated in 150 non-CDH neonates.

Results

190 CDH neonates were included. Baseline characteristics, echo measurements and outcome data are demonstrated in Table 1.

An optimal cutoff for RVD/LVD of 1.1 to predict clinical endpoints was calculated. The population was divided in group 1 (RVD/LVD ≥1.1) and group 2 (RVD/LVD < 1.1). 41 neonates (46.7%) in group 1 and in 13 patients (12.7%) in group 2 (P<0.001) died. 61 patients (69.3%) in group 1 and 25 patients (24.5%) in group 2 met the secondary endpoint (P < 0.001). In patients with an RVD/LVD ≥1.1 the relative risk of death and ECMO/early death was 3.57 and 2.78, respectively. Using Cox regression, an RVD/LVD ≥1.1 was independently associated with mortality (HR 2.32, 95%CI: 1.17-4.59; P=0.016). In non-CDH neonates an RVD/LVD between 0.8 and 1.1 can be considered normal independently of gestational age.

Conclusion

We evaluated a novel, easily obtainable echocardiocardiographic parameter to identify high-risk CDH neonates during the early postnatal period. An RVD/LVD ≥1.1 is independently associated with poor outcome and reflects both, LV hypoplasia and RV enlargement in CDH neonates.

Images

Variables		Group 1 $RV_D / LV_D \geq 1.1$ (n=88)	Group 2 $RV_D / LV_D < 1.1$ (n=102)	*p-value*
Demographics				
Gender (male), n (%)		54 (61.4%)	57 (55.9%)	0.446
Gestational age (weeks), median [IQR]		37.4 [35.1-38.6]	38 [36.7-39.0]	**0.045**
Birthweight (Kg), median [IQR]		2.7 [2.3-3.3]	3.0 [2.5-3.3]	**0.04**
Defect size, n (%)	A	1 (1.1%)	13 (12.7%)	**<0.001**
	B	16 (18.2%)	36 (35.3%)	
	C	26 (29.5%)	36 (35.3%)	
	D	23 (26.1%)	11 (10.8%)	
	Not repaired	22(25.0%)	6 (5.9%)	
Inborn, n (%)		78 (88.6%)	92 (90.2)	0.814
Age at First echo (hours), median [IQR]		2.4 [1.7-5]	3.7 [2-6.4]	0.020
Major anomalies, n (%)		11 (12.5%)	4 (3.9%)	0.033
Prenatally diagnosed CDH, n (%)		80 (90.9%)	94 (92.1%)	0.977
o/e LHR (28 GW), %, median [IQR]		34 (28-42)	42(35-49)	**<0.001**
Left-sided CDH, n (%)		77 (87.5%)	89 (87.3%)	0.960
Liver-up CDH, n (%)		57 (64.8%)	48 (47.1%)	**0.017**
FETO, n (%)		18 (20.5%)	15 (14.7%)	0.298
Echo parameters				
RV_D/LV_D		1.29 (1.17-1.42)	0.96 (0.88-1.03)	**<0.001**
RV_D/Kg, cm		0.48 (0.41-0.58)	0.39 (0.35-0.46)	**<0.001**
LV_D/Kg, cm		0.37 (0.3-0.4)	0.43 (0.3-0.4)	**<0.001**
Cardiac dysfunction				
No cardiac dysfunction, n (%)		13 (14.8%)	46 (45.1%)	**<0.001**
Right cardiac dysfunction, n (%)		25 (28.4%)	30 (29.4%)	0.879
Left cardiac dysfunction, n (%)		2 (2.3%)	3 (2.9 %)	0.775
Biventricular cardiac dysfunction, n (%)		48 (54.5%)	23 (22.5%)	**<0.001**
Pulmonary hypertension (PH)				

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Pathophysiological phenotypes in CDH: frequency and relationship to disease severity

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Background
CDH is characterised by three underlying pathophysiologies: 1) pulmonary hypoplasia resulting in ventilatory compromise, 2) pulmonary hypertension leading to hypoxia and right ventricular (RV) dysfunction, and 3) left ventricular hypoplasia and dysfunction. However, the relative contribution of these to individual patient phenotype is not routinely characterised in clinical or research settings.

This study aimed to describe the frequency and nature of early pathophysiological phenotypes in CDH and relationships to disease severity.

Methods
Retrospective single-centre cohort analysis of eligible CDH cases between 2017-2021. Phenotypic categories were based on physiological and echocardiographic parameters in the first 24 hours of life using previously described cut-off values:

- Pulmonary hypoplasia (PHypo): lowest pCO2 ≥ 60 mmHg (8 kPa) 1
- Pulmonary hypertension (PH): PDA shunt bidirectional or right-to-left AND either pre-ductal SpO2 ≤ 85% OR RV dysfunction (tissue Doppler RV E' ≤ 4.6 cm/sec or RV Global Longitudinal Strain (GLS) ≤ -14% 2,3
- LV dysfunction (LV Dysfx): LV global longitudinal strain (GLS) ≤ -16% 2

Uncategorized cases were labelled "mild" CDH. Outcomes were compared between phenotypic subgroups.

Results
56 eligible cases were included. Phenotypic subgroups in order of frequency were "PH + LV Dysfx" (41%), "PH only" (32%), "PH + PHypo + LV Dysfx" (12%) , "Mild CDH" (11%), and "LV Dysfx" (4%), Figure 1. No other phenotypes were present.

"PH + PHypo + LV Dysfx" phenotype was associated with right-sided CDH, lower fetal lung volumes, and stage CD defects (100%). This phenotype also exhibited higher mortality (29%), ECMO use (57%) and duration of ventilation compared to other phenotypes. ECMO was not used in cases with "mild CDH" or "PH only".

Conclusions
CDH patients exhibit variable severity of early pulmonary hypertension, cardiac dysfunction and ventilation failure.

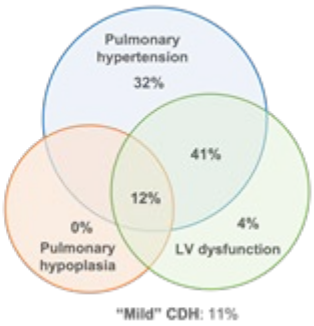
Images

Table 1: CDH Phenotypes: demographics and outcomes

	CDH Phenotype in first 24 hours of life					P value
	Mild	PH only	LV Dysfx only	PH + LV Dysfx	PH + PHypo + LV Dysfx	
N (%)	6 (11)	18 (32)	2 (4)	23 (41)	7 (12)	-
Left sided CDH n (%)	4 (6)	18 (100)	2 (100)	21 (91)	3 (43)	**<0.01**
Defect stage C or D n (%)	1 (20%)	8 (44)	2 (100%)	14 (61)	6 (100)	**0.02**
O:E FLV median median (range)	-	45 (32-66)	34 (21-52)	37 (18-50)	27 (19-35)	0.05
Duration of ventilation (days)	10 (4-12)	9 (5-33)	98 (23-173)	15 (6-101)	39 (23-77)	<0.01
Survival n (%)	6 (100)	18 (100)	2 (100)	20 (87)	5 (71)	0.11
ECMO n (%)	0 (0)	0 (0)	2 (100)	8 (35%)	4 (57%)	**<0.01**

O:E FLV; observed:expected fetal lung volume. ECMO; extra-corporeal membrane oxygenation.
Continuous data summarised as median (range).

Figure 1: CDH Phenotypes



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Clinical and Cellular Sexual Dimorphism in Congenital Diaphragmatic Hernia

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Background:
Congenital diaphragmatic hernia (CDH) is a characterized by pulmonary hypoplasia and pulmonary hypertension (PH), which is thought to be due to endothelial dysfunction. Sexual dimorphism in CDH-PH has yet to be examined from both clinical and cellular perspectives, in part due to lack of an appropriate model. However, we have previously demonstrated that human umbilical vein endothelial cells (HUVECs) provide a robust in vitro model for studying CDH-PH. We hypothesize that males have worse clinical PH outcomes than females, which may be attributed to endothelial dysfunction at the cellular level.

Methods:
A single-center retrospective cohort study was performed for CDH patients from 2008-2020. Patients who underwent prenatal intervention were excluded. Patients were stratified by TOTAL trial definitions of CDH severity. Demographics, extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide (iNO) use, and outcomes (tracheostomy, survival at discharge, and PH resolution at one year) were measured. HUVECs were isolated from 6 CDH subjects, and scratch-wound migration and branching assays were performed. Statistical analyses were performed with logistic regression and unpaired t-tests.

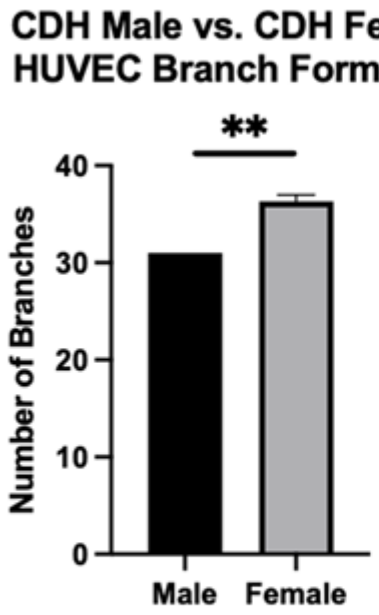
Results:
291 CDH patients were included in the study with male predominance (57%). When controlling for severity, there were no sex-based differences in iNO use (p=0.02), survival (p=0.70) or tracheostomy at discharge (p=0.39), however, females were less likely to require ECMO (p=0.03). Among 89 patients with available echocardiogram data, females had significantly more PH resolution (p=0.03) on echocardiogram at one year. Female CDH HUVECs exhibited increased migration (p=0.04) and branch formation (p<0.01) relative to males(Figure1).

Conclusions:
Using our database of patients treated under the same protocol, we show that males have worse CDH-PH-related outcomes. These differences were also seen at the cellular level, with males exhibiting increased endothelial dysfunction relative to females. Further understanding of this sexual dimorphism will help in the development of tailored therapies to treat CDH-PH.

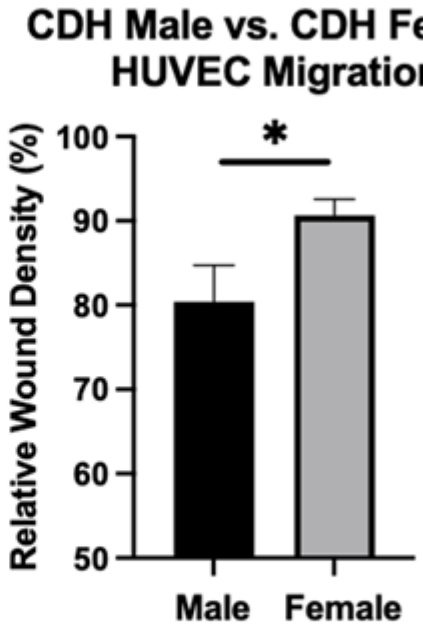
Images

Figure 1

A.



B.



A: CDH Male vs. CDH Female HUVEC branch formation assay shows significantly increased number of branch formation compared to males. **B:** CDH Male vs. CDH Female HUVEC scratch-wound migration assay shows significantly increased migration among female CDH HUVECs compared to males.