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Right Ventricular Strain, Brain Natriuretic Peptide, and Mortality in Congenital Diaphragmatic Hernia.

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ORIGINAL RESEARCH

Right Ventricular Strain, Brain Natriuretic Peptide, and Mortality in Congenital Diaphragmatic Hernia

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Abstract

Rationale: Brain-type natriuretic peptide (BNP) correlates with pulmonary hypertension as demonstrated by echocardiogram in congenital diaphragmatic hernia (CDH); however, its association with right ventricular (RV) function and mortality is unknown.

Objectives: To characterize the relationships between echocardiogram-derived RV strain, BNP, and mortality in diaphragmatic hernia.

Methods: We performed a single-center retrospective cohort study of infants with CDH and at least one BNP–echocardiogram pair within a 24-hour period. RV global longitudinal strain (GLS) and free-wall strain (FWS) were measured on existing echocardiograms. Associations among strain, BNP, and mortality were tested using mixed-effect linear and logistic regression models. Survival analysis was stratified by BNP and strain abnormalities.

Results: There were 220 infants with 460 BNP–echocardiogram pairs obtained preoperatively ($n = 237$), ≤1 week postoperatively ($n = 35$), and >1 week postoperatively ("recovery"; $n = 188$). Strain improved after repair ($P < 0.0001$ for all periods). Higher BNP level was associated with worse strain in recovery but not before or immediately after operation (estimate [95% confidence interval] for recovery: GLS, 1.03 [0.50–1.57]; $P = 0.0003$; FWS, 0.62 [0.01–1.22]; $P = 0.047$). BNP and strain abnormalities were associated with an extracorporeal-membrane oxygenation requirement. Higher BNP level in recovery was associated with greater mortality (odds ratio, 11.2 [1.2–571.3]; $P = 0.02$). Abnormal strain in recovery had high sensitivity for detection of mortality (100% for GLS; 100% for FWS) but had low specificity for detection of mortality (28% for GLS; 48% for FWS).

Conclusions: Persistent RV dysfunction after CDH repair may be detected by a high BNP level and abnormal RV strain.

Keywords: congenital diaphragmatic hernias; pulmonary hypertension; heart; ventricles; pediatrics

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Neonates and infants with pulmonary hypoplasia due to congenital diaphragmatic hernia (CDH) may experience life-threatening pulmonary hypertension and right ventricular (RV) failure. Maldevelopment of the pulmonary vasculature results in elevated pulmonary vascular resistance and pulmonary artery pressure (1), which are poorly tolerated by the right ventricle. Despite surgical advances, CDH morbidity and mortality are high and have been attributed to pulmonary hypoplasia and pulmonary hypertension (2, 3).

In CDH, treatment of pulmonary hypertension and RV failure may be guided by the echocardiogram and brain-type natriuretic peptide (BNP), a peptide secreted by the cardiac myocytes in response to pressure overload (4). BNP is a well-established marker of ventricular strain in adults with heart failure (5) and pulmonary hypertension (6) and correlates with the presence of pulmonary hypertension in CDH (7). In adults with pulmonary arterial hypertension (PAH), BNP increases with RV dysfunction and is associated with mortality (8, 9). However, the relationships among BNP, quantitative measures of RV function, and CDH mortality are unknown.

Qualitative ventricular dysfunction by standard two-dimensional echocardiographic imaging was a critical determinant of mortality in a CDH registry–based study (10). Quantitative assessment of RV function is challenging because of the right ventricle's pyramidal geometry, anterior position in the chest, and altered geometry in disease states (11, 12). More recently, myocardial deformation ("strain") imaging has emerged as a sensitive and accurate geometry-independent method to identify RV dysfunction (13, 14). Strain refers to the change in length of the myocardium relative to its resting length (expressed as a percentage, with more negative values indicating better systolic function). Reference ranges of RV global longitudinal strain (GLS) in healthy children are available (15). In children and adults with PAH, better RV GLS predicts survival (16, 17). In neonates with CDH, RV strain is decreased after delivery (18–20), and worse RV strain is associated with the need for extracorporeal-membrane oxygenation (ECMO) (21).

In clinical practice, an elevated BNP level may suggest worsening pulmonary hypertension and/or RV dysfunction; however, the relationship between BNP and RV strain has not been established in patients with CDH. Therefore, the objectives of this study were to characterize RV GLS and free-wall strain (FWS) in neonates and infants with CDH and to investigate the associations among RV strain, BNP, and mortality.

Methods

Study Cohort

This single-center, retrospective cohort study included all infants ⩽6 months of age with CDH enrolled in the Children's Hospital of Philadelphia Pulmonary Hypoplasia Program between 2005 and 2017 who had at least one echocardiogram and serum BNP test performed within 24 hours of each other. Infants with structural heart disease, other than small atrial or ventricular septal defects, were excluded, as were those with persistent large patent ductus arteriosus with left-to-right shunt. According to our laboratory's standard protocol, a large patent ductus arteriosus is defined as having a measure equal to or larger than the branch pulmonary arteries. Echocardiograms performed while weaning ECMO flow and low-quality images on which strain analyses could not be performed were excluded.

On the basis of the number of patients with CDH enrolled in our Pulmonary Hypoplasia Program database, we estimated that approximately 220 eligible infants would have at least two BNP–echocardiogram pairs per infant, resulting in at least 440 pairs of data. With this sample size, we would have 81% power to detect a partial correlation coefficient of 0.135 between BNP level and RV GLS or FWS with a 5% significance level using multiple linear regression adjusting for other covariates. The study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Clinical Variables

BNP levels and pertinent clinical data were abstracted from the electronic medical record. Quantitative plasma measurement of BNP was performed using a chemiluminescent microparticle immunoassay on an Abbot Architect i2000SR. BNP was considered abnormal if greater than 100 pg/ml, the upper limit of normal for our laboratory.

Echocardiographic Variables

Clinically indicated echocardiograms were performed using standard pediatric views with 3- to 8-MHz transducers on a Phillips IE33 machine in accordance with our echocardiography laboratory's standard imaging protocol, which was consistent over the study period. Images were digitally stored in the Syngo Dynamics system (Siemens). A single pediatric cardiac sonographer (Y.W.) blinded to clinical characteristics obtained offline measures of RV function. Strain measurements were obtained from speckle-tracking analysis of four-chamber cine-loop images including the RV free wall and ventricular septum using Tomtec software (Image Arena 4.6). Values were averaged to calculate RV GLS and FWS (percentages). By convention, strain values are presented as negative numbers, with a higher magnitude of absolute values indicating better systolic function. For example, a strain value of −30% reflects better systolic function than a strain value of −20%. Strain was considered abnormal if it was less than the absolute value of −25% (15). RV systolic function was also assessed by M-mode tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tricuspid annular peak systolic velocity (s') measured by tissue doppler (22). TAPSE *z*-scores (TAPSEZ) were generated from normative data (23, 24). The FAC (percentage) was calculated from the apical four-chamber view as the end-diastolic area minus the end-systolic area divided by the end-diastolic area (25). Pulmonary hypertension was considered present if at least one echocardiographic criterium was identified: *1*) RV pressure greater than one-half the systemic systolic blood pressure estimated from tricuspid regurgitant jet or patent ductus arteriosus (when present) velocity by the modified Bernoulli Equation ($4 \times \text{velocity}^2$) without an estimate of right

Table 1. Infant characteristics ($N = 220$)

	n (%) or Median (IQR)
Sex	
Male	128 (58)
Female	92 (42)
Race	
White	172 (78)
Black	7 (7)
Asian	13 (6)
Biracial	10 (5)
Other	9 (4)
Ethnicity	
Hispanic or Latino	38 (17)
Gestational age, wk	38.4 (37 to 39)
Birthweight, g	3,060 (2,750 to 3,450)
Left sided CDH	184 (83)
Liver herniation	119 (54)
ECMO support	69 (31)
Patch CDH repair	130 (63)
Age at CDH repair, d	13 (6–22)
Death	29 (13)

Definition of abbreviations: CDH = congenital diaphragmatic hernia; ECMO = extracorporeal-membrane oxygenation; IQR = interquartile range.

Table 2. Improvement in BNP, RV strain, and other markers of RV function with CDH repair

Variable	Overall (*n* = 460)	Pre-Op (*n* = 237)	After Repair* (*n* = 223)	Immediate Post-Op (*n* = 35)	Recovery (*n* = 188)	*P* Value†
BNP	231 (65.1 to 671.1)	360.7 (186.9 to 923.6)	92.9 (23.7 to 409.6)	498.7 (175.3 to 1,415.6)	62 (20.7 to 282.3)	<0.0001
RV GLS	−20 (−15.8 to −23.9)	−17.9 (−14.8 to −22.2)	−21.5 (−17.9 to −25)	−19.3 (−15.3 to −23.8)	−21.8 (−18.5 to −25.4)	<0.0001
RV FWS	−22.6 (−18.5 to −27)	−20.5 (−16.5 to −24.4)	−24.6 (−21.1 to −28.5)	−21.9 (−17.9 to −25.3)	−25 (−21.8 to −28.8)	<0.0001
RV FAC, %	37.1 (30.5 to 44.8)	34 (26.8 to 40.8)	40.7 (34.2 to 48)	35.4 (30.1 to 42.9)	41.1 (35.2 to 48.5)	<0.0001
TAPSE, cm‡	0.9 (0.7 to 1.1)	0.7 (0.6 to 0.9)	1.1 (0.9 to 1.3)	0.9 (0.8 to 1.15)	1.1 (0.9 to 1.3)	<0.0001
TAPSEZ	−0.9 (−2.7 to 0.1)	−1.8 (−3.5 to 0.9)	−0.3 (−1.4 to 1.1)	−0.09 (−1 to 1.6)	−0.3 (−1.4 to 1.1)	<0.0001
RV s', m/s§	0.07 (0.06 to 0.09)	0.06 (0.05 to 0.08)	0.09 (0.07 to 0.1)	0.08 (0.06 to 0.09)	0.09 (0.08 to 0.1)	<0.0001
Pulmonary hypertension	225 (95)	225 (95)	118 (53)	28 (80)	9 (48)	<0.0001

Definition of abbreviations: BNP = brain-type natriuretic peptide; CDH = congenital diaphragmatic hernia; FAC = fractional area change; FWS = free-wall strain; GLS = global longitudinal strain; post-op = postoperative; pre-op = preoperative; RV = right ventricular; s' = tricuspid annular peak systolic velocity; TAPSE = tricuspid annular plane systolic excursion; TAPSEZ = TAPSE *z*-score.

Continuous variables are expressed as the median (interquartile range). Categorical variables are expressed as *n* (%).

*Includes both immediate post-op and recovery data.

†*P* value for comparisons among the pre-op, immediate post-op, and recovery periods.

‡For TAPSE/TAPSEZ: overall *n* = 294, pre-op *n* = 147, post-op *n* = 147, immediate post-op *n* = 20, recovery *n* = 127.

§For RV s': overall *n* = 269, pre-op *n* = 134, post-op *n* = 135, immediate post-op *n* = 18, recovery *n* = 117.

atrial pressure, *2*) bidirectional or right-to-left patent ductus arteriosus (or rarely ventricular septal defect) shunt, or *3*) flattened or bowing ventricular septum at end-systole (26). We have previously published high intrarater (for sonographer Y.W.) and interrater intraclass correlation coefficient values of 0.9–0.99 for RV strain and other continuous echocardiographic measures of RV function (27–30).

Statistical Analyses

First, we described the demographic and clinical characteristics of the study cohort. Next, we compared the BNP, strain, and other echocardiographic measurements among different time periods. Then, we assessed the association between BNP level and strain overall and within each time period. Finally, we investigated the relationship between BNP and strain abnormalities and survival. Several subanalyses are also described. A P value < 0.05 was used to define statistical significance.

Cohort Characteristics

Standard descriptive statistics were used to describe infant characteristics, BNP levels, and echocardiographic parameters. Echocardiographic and BNP data were grouped relative to date of CDH repair: preoperative ("pre-op") data (before CDH repair), immediate postoperative ("post-op") data (≤1 wk after CDH repair), and "recovery" data (>1 wk after CDH repair). Another category, "after repair," included both post-op and recovery data. In our clinical experience, many patients have improved hemodynamics and are weaning from cardiorespiratory support about 1 week after CDH repair, so we differentiated the immediate post-op period (≤1 wk after CDH repair) from the later recovery period.

Differences in BNP and Echocardiographic Measures across Time Periods

Kruskal-Wallis tests were used to compare median BNP level and continuous echocardiographic variables among the three time periods using average values for patients with more than one BNP–echocardiogram pair in a given time period. The presence of pulmonary hypertension among the three time periods was compared using mixed-effects logistic regression models.

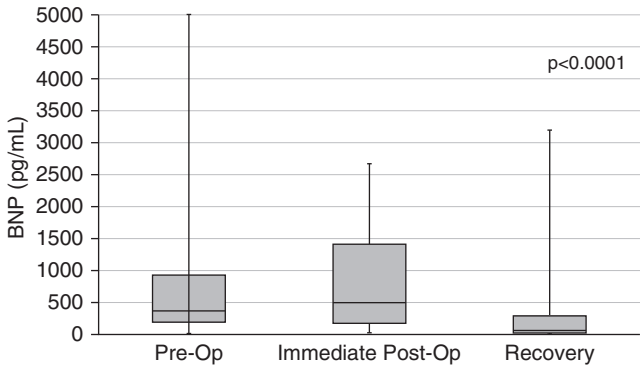

Figure 1. BNP decreases after congenital diaphragmatic hernia repair. The *P* value is for comparisons among the pre-op, immediate post-op, and recovery periods. BNP = brain-type natriuretic peptide; post-op = postoperative; pre-op = preoperaptive.

Relationship between Strain and Other Markers of RV Function, Overall and within Each Time Period

Linear mixed-effect models were used to test the association between strain and other markers of RV systolic function as continuous variables, with strain as the dependent variable. These models included days after surgical repair in post-op regression models.

Relationship between BNP and Strain, Overall and within Each Time Period

Generalized linear mixed-effect models were used to determine the association between BNP level and strain as continuous variables. Logarithmic transformation of BNP was performed. Simple linear mixed models were used to assess the relationship between demographic/clinical variables and strain. Variables included sex, race, ethnicity, gestational age, birth weight, CDH side, presence of liver herniation, history of ECMO, patch repair, age at CDH repair, and days after surgical repair. The variables that were statistically significant at a 0.05 level were adjusted as covariates in the BNP and strain models and included history of ECMO, days after surgical repair, and age at CDH repair. History of ECMO was adjusted as a covariate in the models in all three time periods. Days after surgical repair and age at CDH repair were adjusted as covariates in the post-op regression models. Sensitivity analyses were conducted via stratified models by ECMO requirement. Estimates (95% confidence intervals) were calculated for the regression models in each time period.

Relationship between BNP and Strain Abnormalities and Survival

Logistic regressions were used to test the association between the presence of BNP or strain abnormality and survival. After using simple logistic regression models to test other factors that could affect survival, ECMO and CDH repair age were included in the model as covariates. The sensitivity, specificity, positive predictive value, and negative predictive value of BNP and strain abnormalities in detecting mortality were calculated.

Additional Subanalyses

We also analyzed existing, clinically indicated echocardiograms performed on any patient from the original cohort at 6 ± 1 months of age. Strain and other echocardiographic measures were performed as above. BNP levels obtained within 1 week of the echocardiogram were extracted from the medical record. The associations between BNP level and strain and between strain and other measures of RV systolic function were tested by Spearman correlation. The Wilcoxon rank-sum test was used to compare strain in infants with and without echocardiographic evidence of pulmonary hypertension.

Results

There were 220 infants who met inclusion criteria, resulting in 460 BNP–echocardiogram pairs (range, 1–6 pair(s)/subject). Infant characteristics are shown in Table 1. Most patients were male, born at term, and had left CDH and liver herniation. ECMO was required in 69 (31%) patients, and 33 (7%) BNP–echocardiogram pairs were obtained in subjects while on ECMO. CDH repair occurred at median 13 (interquartile range [IQR], 6–22) days of age and included a patch in more than half of subjects. There were 29 deaths (13%) with 14 (48%) occurring before repair and 15 (52%) occurring at a median of 34 (IQR 7.5–91) post-op days.

There were 237 (52%) BNP–echocardiogram pairs obtained before CDH repair, 35 (8%) pairs obtained ⩽1 week

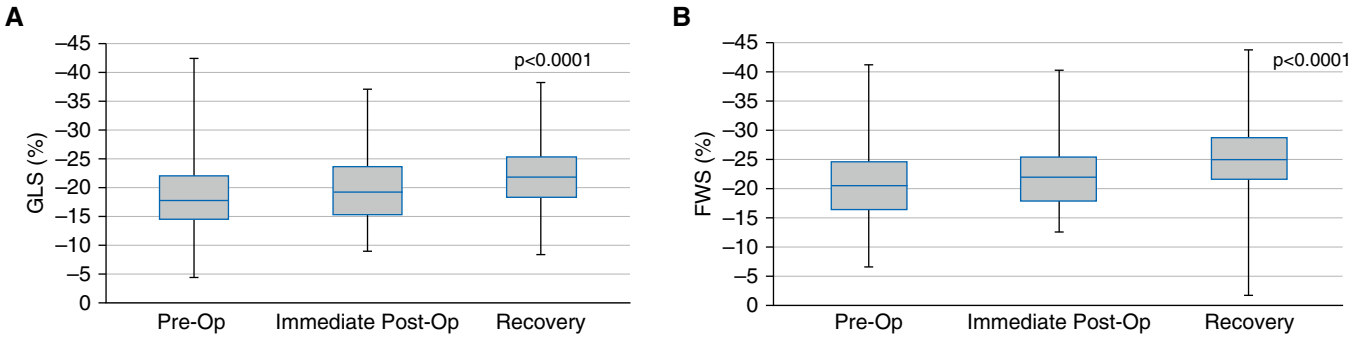

Figure 2. Both (*A*) GLS and (*B*) FWS improve after congenital diaphragmatic hernia repair. *P* value is for comparisons among the pre-op, immediate post-op, and recovery periods. FWS = free-wall strain; GLS = global longitudinal strain; post-op = postoperative; pre-op = preoperaptive.

Table 3. Association between strain and echocardiographic measures of RV function by time period

Dependent Variable	Predictor	Estimate (95% CI); *P* Value*			
		All Data	Pre-Op	After Repair†	Immediate Post-Op	Recovery
GLS	TAPSEZ	−0.88 (−1.19 to −0.58); <0.0001	−0.89 (−1.46 to 0.31); 0.0033	−0.58 (−0.99 to −0.17); 0.006	−0.29 (−1.60 to 1.02); 0.64	−0.70 (−1.14 to −0.26); 0.0024
	RV FAC, %	−0.48 (−0.51 to −0.45); <0.0001	−0.53 (−0.57 to −0.49); <0.0001	−0.42 (−0.47 to −0.37); <0.0001	−0.52 (−0.63 to −0.40); <0.0001	−0.39 (−0.45 to −0.34); <0.0001
	RV s', m/s	−0.85 (−1.19 to −0.51); <0.0001	−0.38 (−1.04 to −0.27); 0.24	−0.58 (−1.09 to −0.08); 0.026	0.20 (−2.65 to 3.04); 0.89	−0.79 (−1.30 to −0.28); 0.0036
	Pulmonary hypertension	4.71 (3.37 to 6.04); <0.0001	2.30 (−3.38 to 7.99); 0.32	3.45 (1.90 to 5.00); 0.0001	−4.08 (−10.05 to 1.89); 0.17	3.47 (1.85 to 5.08); 0.0003
FWS	TAPSEZ	−0.94 (−1.27 to −0.61); <0.0001	−1.01 (−1.60 to −0.42); 0.0013	−0.46 (−0.92 to −0.01); 0.046	−0.21 (−1.43 to 1.02); 0.72	−0.56 (−1.08 to −0.05); 0.03
	RV FAC, %	−0.48 (−0.52 to −0.45); <0.0001	−0.52 (−0.57 to −0.48); <0.0001	−0.40 (−0.46 to −0.34); <0.0001	−0.48 (−0.60 to −0.36); <0.0001	−0.38 (−0.45 to −0.30); <0.0001
	RV s', m/s	−0.85 (−1.20 to −0.49); <0.0001	−0.76 (−1.40 to −0.13); 0.021	−0.08 (−0.66 to −0.50); 0.78	0.09 (−2.69 to 2.88); 0.94	−0.16 (−0.78 to 0.46); 0.61
	Pulmonary hypertension	5.05 (3.64 to 6.46); <0.0001	2.43 (−3.37 to 8.23); 0.31	3.10 (1.41 to 4.80); 0.0009	−3.86 (−9.12 to 2.41); 0.24	3.07 (1.24 to 4.91); 0.0026

Definition of abbreviations: 95% CI = 95% confidence interval; FAC = fractional area change; FWS = free-wall strain; GLS = global longitudinal strain; post-op = postoperative; pre-op = preoperative; RV = right ventricle; s' = tricuspid annular peak systolic velocity; TAPSEZ = tricuspid annular plane systolic excursion *z*-score.
*All *P* values are for comparisons among pre-op, immediate post-op, and recovery periods.
†Includes both immediate post-op and recovery data.

immediately after operation, and 188 (40%) pairs obtained in recovery >1 week after operation. Table 2 and Figures 1 and 2 demonstrate the change in BNP, RV strain, and other echocardiographic parameters with CDH repair. Abnormal BNP was seen in 89% in the pre-op period, 91% in the immediate post-op period, and in 42% in recovery. The presence of abnormal GLS and FWS strain was distributed as follows: pre-op period = 86% and 82%, immediate post-op period = 85% and 76%, and recovery period = 43% and 55%, respectively. BNP, GLS, and FWS all improved after CDH repair ($P < 0.0001$ for all comparisons among time periods).

Worse GLS and FWS were associated with other markers of RV dysfunction. Both were associated with lower FAC in all time periods and with lower TAPSEZ in the pre-op and recovery periods (Table 3). Strain was not consistently associated with RV s' velocity; GLS was associated with RV s' velocity only in recovery, and FWS was associated with RV s' velocity only in the pre-op period. Strain was worse in those with pulmonary hypertension in recovery but was not worse in the pre-op or immediate post-op periods.

BNP and strain were positively associated such that as BNP level increased, strain also increased (lower magnitude of absolute value), which corresponded to a decrease in RV systolic function (Table 4). However, this relationship depended on the time period relative to CDH repair. There was no association between BNP level and strain in either the pre-op or immediate post-op periods, but there was a positive association between BNP level and strain in the recovery period. Higher BNP level was associated with worse strain in recovery (estimates: GLS, 1.03 [0.50–1.57]; $P = 0.0003$; FWS, 0.62 [0.01–1.22]; $P = 0.047$) but not before or after operation.

When the relationships between patient characteristics and BNP/strain abnormalities were tested, a history of ECMO was associated with abnormal BNP and strain after CDH repair (Table 5). No other patient characteristic was associated with abnormal BNP or strain. A subanalysis comparing patients with and without a history of ECMO demonstrated a persistent positive association between recovery BNP level and strain in the patients with a history of ECMO (Table 6). BNP level and strain were still positively associated in patients without a history of ECMO, but the

Table 4. Association between BNP (independent) and strain (dependent variable)

Dependent Variable	Estimate [*β Coefficient (95% CI); P Value*]*				
	All Data (*n* = *460*)	**Pre-Op (*n* = *237*)**	**After Repair† (*n* = *223*)**	**Immediate Post-Op (*n* = *35*)**	**Recovery (*n* = *188*)**
GLS	1.18 (0.82 to 1.55); <0.0001	0.39 (−0.38 to 1.16); 0.32	1.00 (0.50 to 1.49); 0.0001	1.61 (−0.49 to 3.72); 0.13	1.03 (0.50 to 1.57); 0.0003
FWS	1.27 (0.89 to 1.66); <0.0001	0.50 (−0.28 to 1.29); 0.21	0.73 (0.18 to 1.27); 0.0094	1.25 (−0.81 to 3.31); 0.22	0.62 (0.01 to 1.22); 0.047

Definition of abbreviations: 95% CI = 95% confidence interval; BNP = brain-type natriuretic peptide; FWS = free-wall strain GLS = global longitudinal strain; post-op = postoperative; pre-op = preoperative.
*All *P* values are for comparisons among pre-op, immediate post-op, and recovery periods.
†Includes both immediate post-op and recovery data.

association only trended toward significance when examined by time period.

Abnormal BNP after CDH repair was associated with mortality (post-op odds ratio [OR], 12.2 [1.4–638.0]; $P = 0.02$; recovery OR, 11.2 [1.2–571.3]; $P = 0.03$). All deceased patients with available data had abnormal GLS and FWS after CDH repair (Table 7). There was a trend toward significance between abnormal FWS and mortality in the recovery period ($P = 0.097$). In recovery, both GLS and FWS abnormalities were highly sensitive but poorly specific in detecting mortality (GLS: sensitivity of 100%, specificity of 28%, positive predictive value of 8%, and negative predictive value of 100%; FWS: sensitivity of 100%, specificity of 48%, positive predictive value of 11%, and negative predictive value of 100%).

Of the 220 patients, 81 (37%) had an echocardiogram at 6 ± 1 months of age. In these, 29 of 81 (36%) had evidence of pulmonary hypertension and 63 of 81 (78%) had a BNP level. There was no correlation between the median BNP level (18.7 [11.6 to 37.5]; range, 10 to 1,930) and strain (GLS: −26.2 [−22.1 to −29.5]; FWS −28.9 [−25.2 to −32.3]) at 6 months ($P = 0.11$ for GLS; $P = 0.24$ for FWS). GLS was correlated with FAC (Spearman $r = -0.64$; $P < 0.0001$), and FWS was correlated with both TAPSEZ ($r = -0.34$; $P = 0.02$) and FAC ($r = -0.68$; $P < 0.0001$). Strain was worse in patients with pulmonary hypertension (GLS in pulmonary hypertension: −25% [−19 to −27] vs. GLS in nonpulmonary hypertension: −27% [−23 to −30]; $P = 0.018$; FWS in pulmonary hypertension: −27% [−24 to −31] vs. FWS in nonpulmonary hypertension: −30% [−26 to −33]; $P = 0.045$).

Discussion

In this large cohort of neonates and infants with CDH, we demonstrated low initial RV strain with improvement in strain and BNP level after CDH repair. In recovery from CDH repair, higher BNP level was associated with worse RV strain and with mortality. Abnormal RV strain detected mortality with high sensitivity but low specificity. To our knowledge, this is the largest report of RV strain in patients with CDH to date and the first to investigate the relationships among strain, BNP, and mortality. These findings increase our appreciation of the scope of RV dysfunction in CDH and increase our knowledge of strain as a prognostic tool in this population.

Table 5. History of ECMO was associated with abnormal BNP/strain after CDH repair

Dependent Variable (after Repair)	Predictor	Odds Ratio (95% CI)	*P* Value
BNP	ECMO	2.27 (1.05–4.76)	0.038
GLS	ECMO	2.86 (1.27–6.25)	0.013
FWS	ECMO	4.17 (2.13–7.69)	<0.0001

Definition of abbreviations: 95% CI = 95% confidence interval; BNP = brain-type natriuretic peptide; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal-membrane oxygenation; FWS = free-wall strain; GLS = global longitudinal strain.

Several small studies have described abnormal strain in newborns with CDH. RV strain is decreased compared with age-matched control subjects (18, 20) and worse in patients with CDH requiring ECMO than in patients not requiring ECMO (21). In addition, a decreased magnitude of left ventricular (LV) GLS, but not RV strain, in the first 48 hours of life is associated with ECMO and death (19). Similar to authors of other studies, we also found that post-op BNP and strain abnormalities were associated with a history of ECMO (21). However, our study is the first to describe changes in RV strain with CDH repair and beyond the immediate neonatal period. It is concerning that abnormal strain was still seen in approximately half of the cohort after repair. These new data are essential to recognizing persistent RV dysfunction in CDH to develop targeted pharmacologic interventions to improve cardiac function and patient outcomes.

BNP and nonactive N-terminal pro-BNP are strong prognostic indicators in adult and pediatric PAH (8, 9, 31). Although BNP correlates with the presence of pulmonary hypertension in CDH, it does not discriminate pulmonary hypertension severity (7). Our findings demonstrate that the relationship between BNP and RV systolic function may vary on the basis of CDH repair status. The lack of association between BNP level and RV strain in the pre-op period may not be surprising. Pre-op cardiac care may include inotropes, lusitropic agents, pulmonary vasodilators, and prostaglandins to maintain ductus arteriosus patency in the face of severe pulmonary hypertension or RV dysfunction, which may result in differences in RV "load" and BNP level among otherwise similar patients. The small number of BNP–echocardiogram pairs in the immediate post-op period may have affected

Table 6. Association between BNP (independent variable) and strain (dependent variable) for patients with ECMO history ($n = 69$ with 152 BNP-echo pairs) and without ECMO history ($n = 151$ with 308 BNP–echo pairs)

Dependent Variable	Estimate [β Coefficient (95% CI); *P* Value]*				
	All Data	Pre-Op	After Repair†	Immediate Post-Op	Recovery
Patients with ECMO history					
	$n = 152$	$n = 74$	$n = 78$	$n = 12$	$n = 66$
GLS	1.33 (0.64 to 2.03); 0.0002	0.98 (−0.41 to 2.36); 0.16	1.61 (0.79 to 2.44); 0.0004	1.92 (−1.71 to 5.55); 0.27	1.52 (0.66 to 2.37); 0.0012
FWS	1.16 (0.43 to 1.89); 0.0022	1.21 (−0.21 to 2.63); 0.09	0.94 (0.10 to 1.78); 0.029	0.99 (−2.51 to 4.50); 0.54	0.90 (0.03 to 1.78); 0.043
Patients without ECMO history					
	$n = 308$	$n = 163$	$n = 145$	$n = 23$	$n = 122$
GLS	1.12 (0.68 to 1.55); <0.0001	0.10 (−0.84 to 1.03); 0.84	0.52 (−0.11 to 1.15); 0.10	1.36 (−1.52 to 4.24); 0.34	0.50 (−0.21 to 1.20); 0.16
FWS	1.33 (0.87 to 1.79); <0.0001	0.16 (−0.80 to 1.13); 0.74	0.49 (−0.22 to 1.20); 0.17	1.46 (−1.37 to 4.29); 0.30	0.23 (−0.60 to 1.06); 0.57

Definition of abbreviations: 95% CI = 95% confidence interval; BNP = brain-type natriuretic peptide; echo = echocardiogram; ECMO = extracorporeal-membrane oxygenation; FWS = free-wall strain; GLS = global longitudinal strain; post-op = postoperative; pre-op = preoperative.
*All *P* values are for comparisons among pre-op, immediate post-op, and recovery.
†Includes both immediate post-op and recovery data.

the lack of association in that period, however, after 1 week of post-op recovery, there was a significant association between BNP level and RV strain. In our experience, many patients are weaning from cardiorespiratory support after 1 post-op week, and BNP level may then be a more accurate reflection of RV load. The associations among BNP, strain, and mortality in recovery may reflect the utility of BNP as a longer-term marker of RV function and predictor of mortality.

Our findings suggest that close monitoring for RV dysfunction after CDH repair is warranted and that management of RV dysfunction could improve patient outcomes. Members of our group previously reported early and sustained improvement in RV GLS in 47 children with pulmonary hypertension from various causes, including some with CDH, after initiation of treprostinil (27). In that study, BNP level also improved with treatment, although the relationship between BNP and strain was not investigated. The effects of vasodilator therapies on RV strain and patient outcomes in CDH should be further investigated to determine whether the treatment effect can be measured by improvement in RV strain.

Finally, 36% of patients who had undergone an echocardiogram at 6 months had evidence of pulmonary hypertension. BNP levels were generally normal, although this may have reflected pulmonary vasodilator treatment. The lack of correlation between BNP level and RV strain at 6 months may be due to the lack of variability in BNP. However, RV strain was worse in patients with pulmonary hypertension than in those without pulmonary hypertension. The prognostic implications of this difference warrant further evaluation, but this is consistent with prior reports of decreased RV strain several years after CDH repair (32). These findings support the need for continued surveillance of ventricular function in these patients.

Limitations

Our study is limited by its retrospective nature. We only included patients with high-quality images on which strain could be measured retrospectively. We included patients with BNP–echocardiogram pairs performed within 24 hours of each other, so we cannot exclude management changes in response to one measure that would have affected the other. The scope of the study did

Table 7. Strain abnormalities in deceased patients versus survivors

	Abnormal GLS	Abnormal FWS
After repair*		
Deceased, $n = 10$	10 (100%)	10 (100%)
Alive, $n = 134$	103 (77%)	71 (57%)
P value, exact logistic regression	0.29	0.12
Recovery		
Deceased, $n = 8$	8 (100%)	8 (100%)
Alive, $n = 122$	88 (72%)	63 (52%)
P value, exact logistic regression	0.29	0.097

Definition of abbreviations: FWS = free-wall strain; GLS = global longitudinal strain.
*Includes patients with abnormal strain in either immediate postoperative or recovery periods.

not allow us to assess the effect of management strategies on strain or the BNP–strain relationship, but this should be tested in future prospective studies. Most of our analyses were not significant during the immediate post-op period. This could be due to the small number of BNP–echocardiogram pairs in that time period. Finally, LV systolic dysfunction is an important prognostic indicator in CDH. Future studies should describe LV strain over time and investigate the association among BNP, LV strain, and outcomes.

Conclusions

In conclusion, RV dysfunction, as reflected by a lower magnitude of RV strain, improves with CDH repair but persists in many patients. Higher BNP level is associated with worse RV strain and with mortality during recovery from CDH repair. Strain abnormalities are associated with mortality with high sensitivity; therefore, normal strain values are reassuring. BNP and strain should be followed closely after CDH repair, and appropriate management of RV dysfunction is warranted. Future interventions targeting RV dysfunction in this population may help improve survival in patients with CDH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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