Mid-term differences in right ventricular function in patients with congenital diaphragmatic hernia compared with controls

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Original article

Background: **Patients with congenital diaphragmatic hernia (CDH) may have abnormal lung development, which may cause detrimental effects on right ventricular (RV) function. This study aimed to determine if there are persistent echocardiographic differences in RV function in patients with CDH years after repair versus control patients.**

Methods: **Patients who underwent repair for CDH were recruited. RV function was evaluated by strain analysis and tissue Doppler imaging (TDI). Wilcoxon's rank-sum test was used for analysis.**

Results: **Seven CDH patients and 16 control patients were studied. There was no difference in age between the CDH and control groups (6.2±1.7 years *vs.* 5.7±1.7 years). TDI demonstrated significantly lower values in the RV early diastolic wave (12.8±1.5 cm/s *vs.* 16.1±3.1 cm/s) and RV systolic wave (10.2± 0.8cm/s *vs.* 13.4±1.3 cm/s) when comparing the CDH group and the control group. Interventricular apical septal strain was significantly lower in the CDH group than in the control group (-20.1±4.6% *vs.* -25.4±4.1%). There was a trend towards lower strain values in the RV mid-lateral segment in the CDH group (-30.8±9.9% versus -39.7±6.0%, *P*=0.06) and a lower global RV strain (-27.8±3.0% *vs.* -31.1±3.1%, *P*=0.06).**

Conclusions: **Patients who underwent CDH repair continue to have differences in RV function years after repair. Follow-up is needed to determine how these differences impact cardiac function in adult survivors of CDH.**

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Introduction

Patients born with congenital diaphragmatic hernia (CDH) may have abnormal pulmonary artery development which can contribute to numerous short and long-term sequelae.[1-3] Pulmonary hypertension is a frequent problem in patients with CDH in the newborn period which may persist in certain children and require long-term follow-up and various medical therapies.[4] Pulmonary hypoplasia and pulmonary hypertension have detrimental effects on the function of the right ventricle (RV).[5]

Quantification of the RV function is challenging by 2-dimensional echocardiographic techniques secondary to the complex anatomy of the RV.[6] In the past, the assessment of RV function has been qualitative in nature. Newer echocardiographic modalities such as tissue Doppler imaging (TDI), myocardial strain, and strain rate have been used to assess RV function in multiple clinical situations, including both congenital and acquired heart disease.[7-9] These techniques are important because they allow for quantitative assessment of RV function without geometric assumptions. Recent studies have also demonstrated the role of these modalities in patients with pulmonary hypertension.[10-13]

The mid-term effect of pulmonary hypoplasia associated with CDH on RV function has not been assessed. This study was undertaken to determine if there were echocardiographic differences in RV function in patients with CDH years after repair compared with normal controls.

Methods

The institutional review board of the hospital approved

this study and informed consent was obtained for eligible participants. Patients who underwent neonatal repair for CDH were recruited to participate in the study. Age-matched patients without systemic disease were enrolled as controls. Patients with underlying anatomical cardiac or rhythm abnormalities were excluded. Baseline demographics were recorded as well as any medications currently being used.

Enrolled patients had a standard echocardiography performed, using a Vivid I echocardiographic machine (GE Healthcare).[14] Images were transferred to an off-line workstation (EchoPAC, GE Healthcare) where measurements were performed. All measurements were made in triplicate. Patient information was blinded to the reviewers.

RV end-diastolic diameter at the base of the heart and RV end-diastolic length were measured. The change of RV fractional area (RV FAC) was calculated by the equation: (RV end diastolic area – RV end systolic area)/ RV end diastolic area × 100.[15] The degree of pulmonary and tricuspid regurgitation was also recorded.

Pulsed TDI of the right ventricular free wall was obtained at the level of the tricuspid valve annulus in the apical four chamber view (Fig. 1). The early diastolic wave (e'), atrial contraction wave (a'), and systolic wave (s') were recorded. Myocardial performance index (MPI) of the RV was calculated from the TDI images. MPI was defined as isovolumic relaxation time plus isovolumic contraction time divided by the ejection time.[16,17] This value represents an overall estimate of both systolic and diastolic function of the myocardium.

Longitudinal strain and strain rate values of the RV were obtained. The endocardial border of the RV was traced from the base of the RV free wall to the RV apex and then to the base of the interventricular septum. Frame rates were maximized to optimize strain analysis. A six segment model of the RV was thus achieved and the values of the interventricular (IVS) basal, IVS-mid, IVS-apical, RV lateral-basal, RV lateral-mid, and RV lateral-apical areas were documented (Fig. 2). Global RV strain was also obtained. Global RV strain rates consisting of systolic (S), early diastolic (E) and atrial contraction (A) waves were noted (Fig. 3).

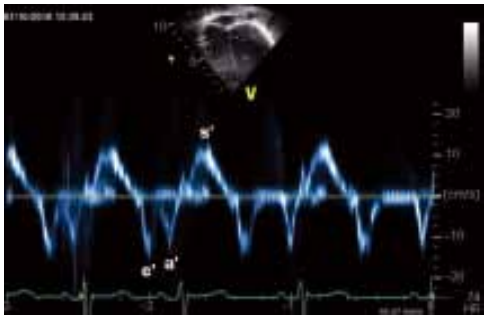

Fig. 1. Pulse tissue Doppler imaging of the right ventricular free wall at the level of the tricuspid valve annulus. **a'**: atrial contraction wave; **e'**: early diastolic wave; **s'**: systolic wave.

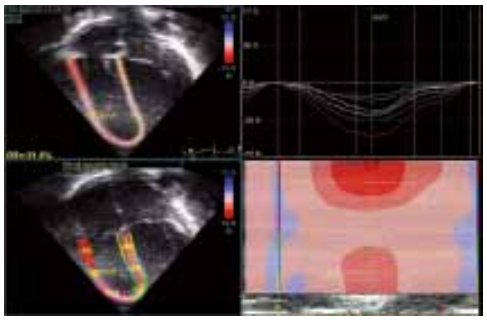

Fig. 2. Six segment model of the right ventricle with longitudinal strain measurements. Top right: AVC (green line), aortic valve closure. White dashed line corresponds to GS or average strain curve. Other color coded curves correspond to different RV segments as seen in the bottom left panel. Bottom right: curved m-mode, color coded panels correspond to different segments. GS: global strain.

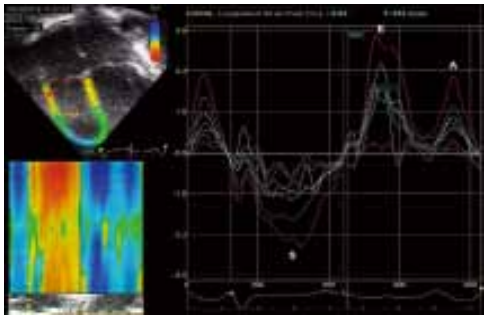

Fig. 3. Global strain rate measurements of the right ventricle. Dotted line is the average of the strain rate for the six segments of the right ventricle. **A**: atrial contraction strain rate; **E**: early diastolic strain rate; **S**: systolic strain rate.

Table 1. Neonatal data of the CDH patients

Patient	Gender	Gestational age (wk)	Birth weight (kg)	Surfactant given	PDA direction pre-repair	Ventilator (d)	NO pre-repair	Oscillator pre-repair	ECMO pre-repair	NO post -repair	Oscillator post-repair	ECMO post-repair	Length of stay (d)
1	Male	37	3.71	No	Bidirectional	21	No	No	No	No	No	No	36
2	Female	40	4.34	No	Left to right	3	No	No	No	No	No	No	13
3	Female	-	3.12	Yes	Bidirectional	18	No	Yes	No	No	No	No	19
4	Male	36	3.30	No	Left to right	5	No	No	No	No	No	No	12
5	Male	37	2.77	No	-	7	No	No	No	No	No	No	40
6	Female	38	2.95	No	Bidirectional	27	Yes	Yes	Yes	Yes	No	No	74
7	Male	39	3.82	No	Bidirectional	58	Yes	Yes	Yes	Yes	No	No	238

CDH: congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; NO: nitric oxide; PDA: patent ductus arteriosus.

Table 2. Baseline demographics at the time of the echocardiogram for CDH and control patients

Variables	CDH group (*n*=7)	Control group (*n*=16)	*P* value
Age (y)	6.2 ± 1.7	5.7 ± 1.7	NS
Weight (kg)	20.6 ± 2.4	21.2 ± 4.9	NS
Heart rate (bpm)	87.7 ± 10.2	87.5 ± 11.7	NS
Gender (M:F)	4:3	9:7	NS

CDH: congenital diaphragmatic hernia; NS: not significant.

Table 3. Tissue Doppler imaging results of the right ventricle

Variables	CDH group (*n*=7)	Control group (*n*=16)	*P* value
TV E (cm/s)	59.2 ± 11.6	61.5 ± 11.7	NS
TV A (cm/s)	36.6 ± 8.0	36.7 ± 10.4	NS
TV E/A	1.7 ± 0.5	1.8 ± 0.4	NS
RV e' (cm/s)	12.8 ± 1.5	16.1 ± 3.1	0.02
RV a' (cm/s)	8.2 ± 1.7	8.7 ± 1.4	NS
RV s' (cm/s)	10.2 ± 0.8	13.4 ± 1.3	<0.01
RV MPI	0.30 ± 0.07	0.34 ± 0.05	NS
RV E/e'	4.7 ± 1.0	4.0 ± 1.3	NS

TV: tricuspid valve; E: early tricuspid valve inflow velocity; A: atrial tricuspid inflow velocity; e': early diastolic wave; a': atrial contraction wave; s': systolic wave; MPI: myocardial performance index; CDH: congenital diaphragmatic hernia; RV: right ventricle; NS: not significant.

Table 4. Strain and strain rates of the right ventricle

Variables	CDH group (*n*=7)	Control group (*n*=13)	*P* value
IVS-basal (%)	-23.6 ± 3.6	-22.0 ± 2.4	NS
IVS-mid (%)	-23.7 ± 2.4	-23.0 ± 2.7	NS
IVS-apical (%)	-20.1 ± 4.6	-25.4 ± 4.1	0.03
RV lateral-basal (%)	-36.3 ± 7.4	-41.4 ± 5.4	NS
RV lateral-mid (%)	-30.8 ± 9.9	-39.7 ± 6.0	0.06
RV lateral-apical (%)	-20.6 ± 13.2	-33.7 ± 3.9	NS
RV global strain (%)	-27.8 ± 3.0	-31.1 ± 3.1	0.06
RV global S strain rate (s^{-1})	-1.8 ± 0.2	-2.0 ± 0.3	NS
RV global E strain rate (s^{-1})	2.6 ± 0.5	2.6 ± 0.5	NS
RV global A strain rate (s^{-1})	1.1 ± 0.3	1.3 ± 0.4	NS

IVS: interventricular septal; RV: right ventricle; S: systolic strain rate; E: early diastolic strain rate; A: atrial contraction strain rate; CDH: congenital diaphragmatic hernia; NS: not significant.

The clinical and echocardiographic data of the study patients in the two groups were compared using Wilcoxon's rank-sum test for continuous variables and the chi-square test for categorical variables. A *P* value <0.05 was considered statistically significant. All continuous variables were reported as means with standard deviations and categorical variables were reported as proportions. The statistical software used for the analysis was SAS version 9.20 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

Seven patients who underwent surgical repair for CDH as neonates were enrolled. Sixteen age-matched patients without systemic disease were enrolled as controls. Initial neonatal data for these patients are shown in Table 1. There were no significant differences in baseline demographics for age, weight, heart rate, or gender between the CDH and control groups (Table 2). No patients were taking any cardiovascular medications. All patients were reported to be in good health by the primary care givers. Three (43%) of the 7 CDH patients were taking pulmonary medications for reactive airways disease. Medications included albuterol and fluticasone for one patient, levalbuterol and montelukast for another patient, and fluticasone, ipratropium, and albuterol for the third patient. No patient in the control group was taking a pulmonary medication.

Echocardiography

Standard echocardiographic images were obtained in all patients. No patient had any evidence of pulmonary hypertension defined as a flattened interventricular septum or a tricuspid regurgitation jet >2.5 m/s. The right and left ventricular function in all the patients was qualitatively normal. There was no more than trivial tricuspid or pulmonary regurgitation in the CDH and control patients. There were no significant differences in the RV end-diastolic diameter at the base of the heart (2.02±0.25 cm *vs.* 1.99±0.26 cm), RV end-diastolic length (3.90±0.37 cm *vs.* 4.14±0.44 cm), and RV FAC (53±6% *vs.* 51±3%) for comparing the CDH group with the control group.

TDI

TDI data were available for all patients. Tricuspid valve inflow velocities were similar between the two groups. The e' and s' were significantly lower in the CDH group than in the control group. The rest of the TDI measured or calculated values were not significantly different between the two groups (Table 3).

Strain and strain rate

Strain and strain rate analysis was available for all seven CDH patients and 13 of the control patients. Three control patients had inadequate images for strain analysis. Six segment RV strain demonstrated significantly lower IVS-apical values in the CDH group than the control group. There was a trend towards lower strain values in the RV lateral-mid segment in the CDH group versus the control group (-30.8±9.9% *vs.* -39.7±6.0%, *P*=0.06). There was also a trend towards lower global RV strain in the CDH group versus the control group (-27.8±3.0% *vs.* -31.1±3.1%, *P*=0.06). There were no other significant differences in the RV lateral and IVS segments or the RV global strain rates between the CDH and control groups (Table 4).

Discussion

Abnormal pulmonary vasculature anatomy and reactivity in patients with CDH causing RV dysfunction is a well described entity during infancy.[12,18] However, no data are available on the possible long-term effects of these pulmonary vasculature abnormalities on the function of the RV. In this study, despite no significant differences in conventional RV echocardiographic parameters, there were significant differences in the TDI and strain results of the CDH group compared with the control group, suggesting decreased RV systolic and diastolic function years after repair.

Decreased RV TDI e' and s' wave velocities in the CDH group suggested persistent early diastolic and systolic abnormalities in the CDH group despite the fact that surgical repair was done in the past. Long-term studies in CDH patients demonstrated no left ventricular functional abnormalities, but RV function was not evaluated in these studies.[19,20] Changes in RV TDI values have been reported pre- and post-CDH repair suggestive of some immediate improvement in RV function.[21] Another study demonstrated persistent differences in RV TDI values in infants with pulmonary hypertension, most of whom had CDH as compared to the control group. The pulmonary hypertension group had significantly lower lateral RV e' and s' wave velocities similar to our findings.[22] The persistence of decreased TDI systolic and diastolic values remote from surgery is consistent with other studies in the pediatric population with chronic pulmonary disease.[23,24]

Echocardiographic strain analysis documented only a significant difference in the IVS-apical segment of the RV between the groups, though the RV lateral-mid and global strain also tended to be lower in the CDH group. Overall, the entire lateral wall of the RV in the CDH group was lower than that in the control group, albeit, not significantly. The lack of significance may be due to the small number of patients evaluated. Unfortunately, we have been unable to enroll more patients given the relatively small number of CDH patients. Despite this shortcoming, the strain differences in the CDH group are still suggestive of lasting RV abnormalities in this population. This finding is akin to other studies documenting decreased strain values in adult patients with pulmonary disease.[10,13,25]

As stated above, multiple studies have shown abnormal RV function in patients with pulmonary disease and this is the likely reason for our findings as well. Pulmonary dysfunction is a well known long-term morbidity in CDH patients.[3,26] Reduced lung perfusion, pulmonary function test, lung volume, and pulmonary blood flow have been documented in elderly CDH patients who were clinically asymptomatic.[19,27] These differences in lung volume and pulmonary vasculature could decrease RV function over time. Three of the CDH patients in this study were on pulmonary medications, but it is likely that all CDH patients would have similar pulmonary abnormalities as shown in the cited studies. We do not have pulmonary anatomical or physiological data to determine if there is an association with the data of RV function, but this seems to be a reasonable speculation.

This study have limitations. The sample size was small, but despite that, significant differences were noted. Only longitudinal RV strain was measured, thus no comment can be made on RV radial or circumferential strain values. Since this is a cross-sectional study, we cannot determine if the RV values have been steadily improving over time as the CDH patients get older, or if they have remained constant or worsened because of ongoing pulmonary abnormalities. As there are no pulmonary variables available, association with cardiac function is purely conjecture at this time. The clinical significance of these RV findings cannot be clearly stated with such a small sample size, but we believe this may serve as a starting point for future studies in this complicated patient population.

In conclusion, this study demonstrated decreased RV function in the CDH patients compared with the controls, using newer echocardiographic techniques. Further research with larger patient cohorts and longitudinal data are necessary to determine if these echocardiographic differences persist over time and if the decreased values are associated with clinical changes.

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Competing interest: None declared.
Contributors: Egan MJ wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. Cua CL is the guarantor.

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