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Ventricular Dysfunction, Interdependence, and Mechanical Dispersion in Newborn Infants with Congenital Diaphragmatic Hernia

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Keywords
Congenital diaphragmatic hernia · Pulmonary hypertension · Myocardial strain · Interdependence · Mechanical dispersion

Abstract
Background: Congenital diaphragmatic hernia (CDH) is an important cause of mortality and morbidity in the neonatal period. Pulmonary hypertension and pulmonary hypoplasia are key pathological findings. Cardiac function may also be an important determinant of disease severity, prognostic indicator, and therapeutic target in CDH. ***Objective:*** The aim of this study was to assess ventricular mechanics and synchrony in infants with CDH and controls using speckle tracking echocardiography (STE). ***Methods:*** Retrospective analysis was performed of echocardiograms obtained in the first 48 h of life in 27 infants with CDH and 20 controls. STE-derived longitudinal strain (LS) was measured in the right and left ventricles (RV, LV). Circumferential strain (CS) and radial strain (RS) were additionally measured in the LV. Mechanical dispersion (MD), a measure of synchrony, was assessed by calculation of the standard deviation of time to peak systolic strain in six ventricular segments. ***Results:*** RV LS and LV LS, LV CS, and LV RS were significantly reduced in CDH compared to controls. In the LV free wall, LS and RS were significantly reduced in CDH. LV LS correlated significantly with RV LS in CDH cases ($r^2 = 0.37$, $p = 0.002$), but not controls ($r^2 = 0.19$, $p = 0.06$). LV LS also correlated with LV MD in CDH ($r^2 = 0.25$, $p = 0.01$) but not controls ($r^2 = 0.02$, $p = 0.54$). ***Conclusions:*** Global impairment of RV and LV systolic function are present in newborn infants with CDH and are associated with primary left ventricular dysfunction, ventricular interdependence, and MD.

Introduction

Congenital diaphragmatic hernia (CDH) is a major cause of mortality in the neonatal period, and morbidity in childhood survivors [1]. Pulmonary hypoplasia and pulmonary hypertension, secondary to abnormal pulmonary vascular development, are key pathological findings. There is growing appreciation that cardiac dysfunction may also play an important role in CDH [2].

In paediatric and adult pulmonary hypertensive disease both right and left ventricular function may be impaired and independently predict outcome [3]. Mecha-

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nisms of ventricular interdependence and altered myocardial synchrony (mechanical dispersion; MD) contribute to ventricular dysfunction in these settings, and may also be important in CDH. Improved understanding of cardiac function in adult pulmonary hypertension has been possible due to advances in non-invasive imaging, including speckle tracking echocardiography (STE) [4]. STE has also been demonstrated to be feasible in newborn infants, allows assessment of regional and global myocardial function, and MD (synchrony) without the limitations of traditional geometric and velocity-based measures [5].

This study utilised STE to assess cardiac mechanics in CDH. We hypothesised that biventricular function, interdependence, and synchrony are impaired in newborn infants with CDH. Improved understanding of cardiac dysfunction in CDH may lead to improved clinical prognostication, targeted therapy, and outcomes.

Methods

Study Population

This case-control study included infants with CDH admitted to the Royal Hospital for Children, Glasgow, UK between January 2015 and January 2018. This is a national referral centre for CDH management including extra-corporeal membrane oxygenation (ECMO) therapy.

CDH cases were managed by a multi-disciplinary team according to an institutional treatment protocol, in accordance with international guidelines [6]. This includes a "gentle" ventilation strategy, targeted use of pulmonary vasodilators (inhaled nitric oxide, sildenafil), cardiotropes (including dopamine, milrinone, and epinephrine), and selective use of ECMO.

A convenience control group was identified of infants with oesophageal atresia (OA) treated at the study centre during the study period. These infants have echocardiographic assessment performed in the first 48 h of life. Only infants who were breathing spontaneously in air, without clinical or echocardiographic evidence of pulmonary hypertension or congenital cardiac anomaly (including ventricular septal defect), were included. In view of potential limitations of the use of OA cases as controls, we additionally compared CDH group strain data to available existing published normative strain data (left ventricle [LV] longitudinal strain [LS], LV circumferential strain [CS], right ventricle [RV] LS) obtained in healthy newborn infants in the first 48 h of life (published controls group) [7, 8]. Study ethical approval was provided by the institutional Information Governance and Research Office.

Demographic Data

Data were collected from the electronic patient records: sex, gestation and weight at birth, and mode of delivery. In the CDH group cardiotropes and pulmonary vasodilators were recorded.

Echocardiographic Assessment

Echocardiographic examination was performed within 48 h of life to assess cardiac function and pulmonary artery pressure (PAP). Echocardiograms were obtained by 2 experienced observers (N.P. and E.F.), using a GE Vivid E9 with a 6-MHz probe, and analysed using Echopac software incorporating QLab (GE Medical, Milwaukee, WI, USA). Echocardiograms were collected using an institutional protocol including optimisation of images for STE analysis. Post-acquisition analysis was performed by a single observer (A.C.M.) using an established analysis protocol, and blinded to group allocation. STE was used to assess peak systolic strain and MD (synchrony) of ventricular segments in accordance with existing consensus recommendations [5].

Analysis was performed from grey-scale 2-dimensional cine-loops, acquired in the 4-chamber LV and RV focused apical views (for LV and RV LS) and 2-chamber short-axis view at mid-ventricle level (for LV circumferential and radial strain; RS). Images with an optimised frame rate:heart rate ratio were selected for analysis [9]. The endocardial border was traced at end-systole to generate a region of interest, adjusted for optimal myocardial tracking. Images with poor tracking were excluded from the analysis. The software generates six segmental strain curves and a combined strain curve (in longitudinal and circumferential planes). From each curve, peak systolic strain (prior to outlet valve closure) was measured to provide segmental, free wall (3 segments), septal (3 segments), and combined (6 segments) strain in the longitudinal plane (LS) in both ventricles, and circumferential (CS) and radial (RS) planes in the LV only. Septal (3 segments) LS was assessed separately in both the RV and LV, as previously reported [10]. To assess MD, we calculated the standard deviation of the time to peak systolic strain in all six segments (in each plane), and corrected for the R-R interval [11]. Longitudinal MD was also assessed in the four non-apical segments only (MD4), in view of previous reports of high interobserver variability and manufacturer recommendations [12].

PAP was assessed by measurement of peak tricuspid regurgitation velocity (TR), when present, inserted into a modified Bernoulli equation to derive estimated peak RV systolic pressure ($RVSP_{EST}$). As TR is not consistently present in CDH, PAP was also assessed by Doppler interrogation of patent ductus arteriosus (PDA) flow. PDA flow was classified as left-to-right, bidirectional, or exclusively right-to-left. In addition, the velocity-time integer of left-to-right and right-to-left flow components of PDA flow were manually traced and a ratio calculated ($VTI_{L:R}$) to quantify PAP. The septal position was classified in end-systole from short-axis views as normal, flattened, or leftward shift. Septal flattening was quantified by calculation of the end-systolic eccentricity index, the ratio of LV major and minor axes dimensions in the short-axis view.

Statistical Analysis

Demographic data are summarised as the median (range). Echocardiographic data were assessed for normality using the Kolmogorov-Smirnov test, and expressed as the mean (SD). Myocardial strain in CDH and controls were compared using the unpaired *t* test. Pearson correlations were assessed between LV and RV function (as a measure of ventricular interdependence) and between ventricular strain measures of PAP and MD. Intra- and interobserver variability of strain and MD measures were assessed by blinded, independent analysis of ten random studies, selected from the CDH group, by 2 study investigators (A.C.M. and N.P.). Intraclass correlation coefficient, Bland-Altman analysis of agreement (bias and 95% limits of agreement), and coefficient of varia-

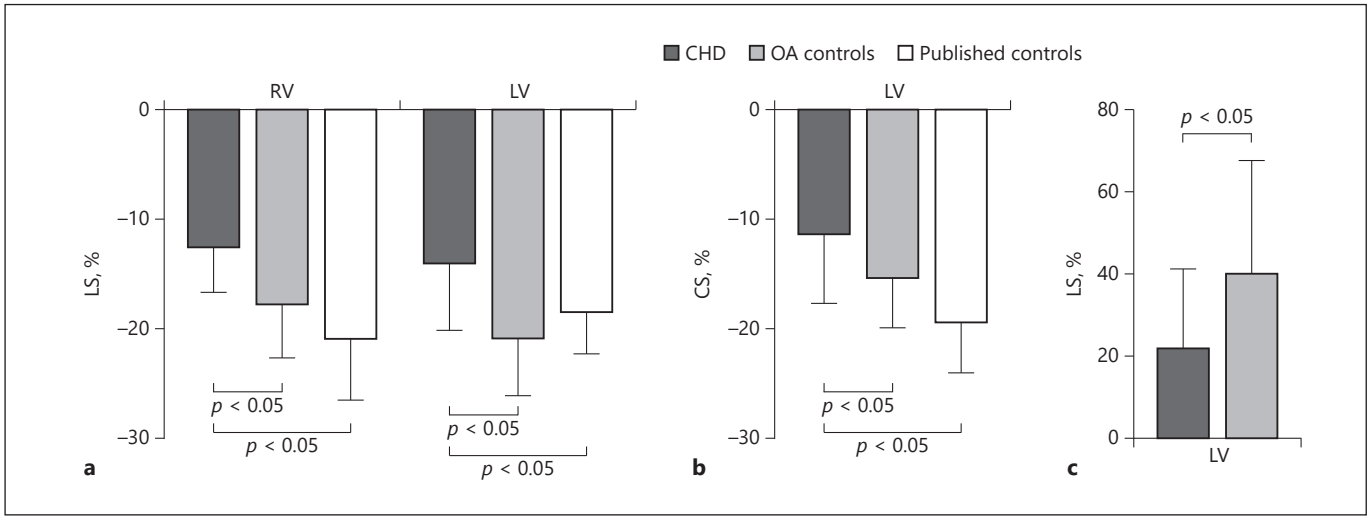

Fig. 1. Myocardial strain in the RV and LV in the CDH and control groups. LV and RV LS in CDH versus controls (**a**), LV CS in CDH versus controls (**b**), and LV RS in CDH versus controls (**c**).

Table 1. Demographic data for the CDH and control groups

	CDH group (n = 25)	Control group (n = 20)	p
GA, weeks	38 (34–42)	39 (33–41)	0.87
Weight at birth, g	3,061 (1,950–3,880)	2,994 (2,070–3,840)	0.5
Male/female	16/9	12/8	0.78

Data are presented as the median (range) and number. CDH, congenital diaphragmatic hernia; GA, gestational age.

tion (COV) were calculated (COV = standard deviation of absolute difference between repeated measures/mean of all repeated measures). Analysis was performed using Prism 7 (GraphPad Software, La Jolla, CA, USA). A p value <0.05 was considered significant. Statistical support was provided by an experienced statistician.

Results

Demographic and Treatment Data

Twenty-seven CDH cases and 20 OA controls were included. Two CDH cases were excluded due to insufficient echocardiographic data. Echocardiographic data were collected at a median of 8 h (range 2–41) of life in the CDH group and a median of 11 h (range 4–24) in the OA control group (p = 0.2). There were no significant differences in baseline demographic data (Table 1).

Eight (32%) cases received ECMO. All echocardiograms were performed prior to ECMO therapy in these cases. Twenty-three CDH cases (92%) received cardiotropes. The same proportion received inhaled nitric oxide, of which 16 (64%) also received intravenous sildenafil.

PAP and Septal Position

Sixteen infants in the CDH group (64%) had measurable peak TR velocity. The mean $RVSP_{EST}$ was 50 (18) mm Hg. A patent arterial duct was present in 21 (84%) of the CDH cases, flow was bidirectional in 17 (68%) cases, right-to-left in 3 cases (12%), and left-to-right in 1 case (4%). The mean PDA $VTI_{L:R}$ was 1.35 (2.1).

In CDH cases the interventricular septum was flattened in 12 (48%) and displaced leftward in 8 (32%). The LV end-systolic eccentricity index was elevated in the CDH group compared to OA controls: 1.5 (0.4) versus 1.3 (0.1; p < 0.001).

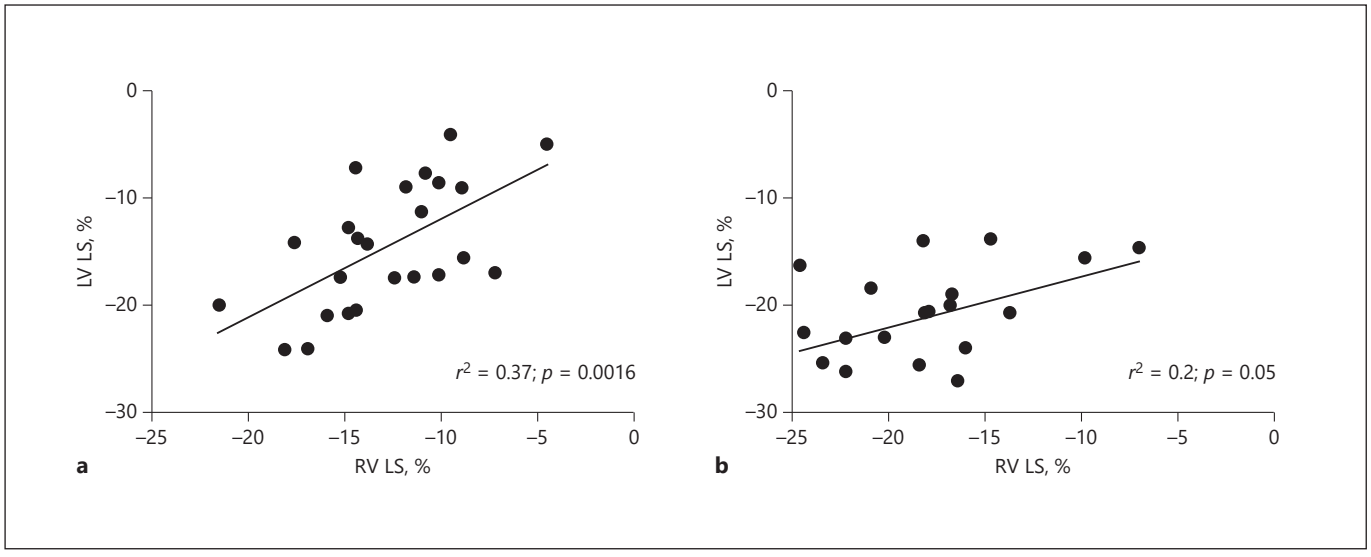

Fig. 2. Correlation of RV and LV LS in the CDH (**a**) and control (**b**) groups.

Table 2. Ventricular strain and synchrony in CDH cases and controls

	CDH (n = 25)	OA controls (n = 20)	p	Published controls [7, 8]	p
RV LS and synchrony					
RV LS all segments, %	−12.8 (3.9)	−18.1 (4.6)	<0.001	−21.2 (5.3)	<0.001
RV LS FW, %	−13.5 (4.9)	−19.5 (4.3)	<0.001	–	–
RV LS septum, %	−10.2 (4.9)	16.9 (6.3)	<0.001	–	–
RV LS-MD, ms	0.95 (0.74)	1.06 (0.80)	0.64	–	–
RV LS-MD4, ms	0.99 (0.83)	0.79 (0.56)	0.35	–	–
LV LS and synchrony					
LV LS all segments, %	−14.3 (5.8)	−21.2 (5)	<0.001	−18.8 (3.5)	0.001
LV LS FW, %	−15.1 (5.69)	−20.6 (6.8)	0.013	–	–
LV LS septum, %	−15.4 (7.95)	−23.3 (4.9)	<0.001	–	–
LV LS-MD, ms	1.3 (0.8)	1.07 (0.6)	0.27	–	–
LV LS-TMD4, ms	1.42 (0.91)	1.14 (0.68)	0.25	–	–
LV CS and synchrony					
LV CS, %	−11.6 (6.1)	−15.6 (4.2)	0.03	−19.7 (4.3)	<0.001
LV CS FW, %	−10.4 (6.2)	−13.4 (7.0)	0.19	–	–
LV CS septum, %	−16.1 (7.9)	−22.6 (7.9)	0.01	–	–
LV GCS-MD, ms	1.73 (0.59)	1.59 (0.8)	0.32	–	–
LV RS and synchrony					
LV RS, %	22.4 (19)	40.7 (26.8)	0.03	–	–
LV RS FW, %	17.7 (21.1)	40.2 (29.8)	0.01	–	–
LV RS septum, %	27.2 (20.5)	41.2 (27.0)	0.07	–	–
LV GRS-MD, ms	0.63 (0.67)	0.42 (0.56)	0.32	–	–

Data are presented as the mean (SD). RV, right ventricle; LV, left ventricle; LS, longitudinal strain; FW, free wall strain; MD, mechanical dispersion, standard deviation of time to peak strain in six ventricular segments; MD4, standard deviation of time to peak longitudinal strain in four non-apical ventricular segments; CS, circumferential strain; RS, radial strain; GCS, global CS; GRS, global RS.

Ventricular Function

LV LS and RV LS were obtained in 25 CDH cases. LV CS and LV RS could not be obtained in 9 cases due to suboptimal image quality. All strain parameters were significantly reduced in the LV (LV LS, RS, CS) and RV (RV LS) compared to OA controls (Fig. 1). LV LS, LV CS, and LV RS were reduced in CDH compared to the published controls (Table 2). Segmental analysis demonstrated significantly reduced LS and CS in the LV septum, and reduced LS and RS in the LV free wall in the CDH group compared to OA controls (Table 2).

Correlation between LV, RV Function, and PAP

RV LS correlated significantly with LV LS in CDH cases ($r^2 = 0.37$, $p = 0.002$), but not in controls ($r^2 = 0.19$, $p = 0.06$; Fig. 2). RV LS was also correlated with LV CS in CDH cases ($r^2 = 0.31$, $p = 0.02$) but not controls ($r^2 = 0.06$, $p = 0.38$). There were no significant correlations between RV or LV strain measures and PDA $VTI_{L:R}$ or $RVSP_{EST}$.

Ventricular Synchrony

Measures of intraventricular synchrony in both the RV and LV were not statistically significantly different between CDH cases and controls (Table 2). LV LSMD correlated with LV LS in CDH cases ($r^2 = 0.25$, $p = 0.01$) but not in OA controls ($r^2 = 0.02$, $p = 0.54$; Fig. 3). RV LS did not significantly correlate with RV LSMD in CDH cases ($r^2 = 0.13$, $p = 0.09$) or controls ($r^2 < 0.001$, $p = 0.97$). Neither RV LSMD nor LV LSMD correlated significantly with PDA $VTI_{L:R}$ or $RVSP_{EST}$.

Observer Variability

Intra- and interobserver variability were comparable, both for RV and LV measures (Table 3). Variability was greatest for LV RS.

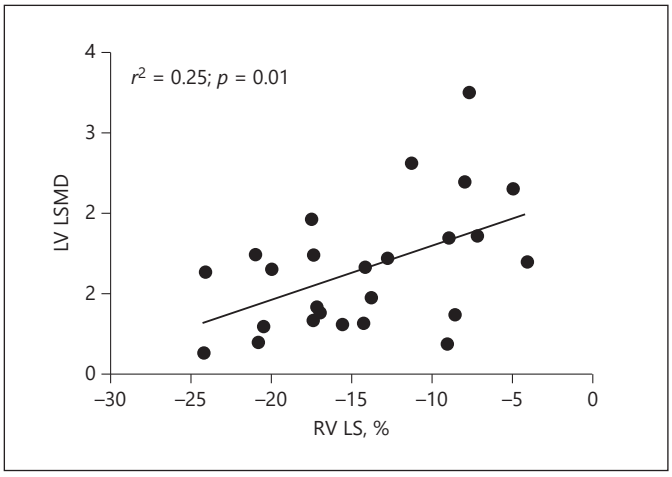

Fig. 3. LV LS versus LV MD in CDH. LV synchrony and LV LS in the CDH group.

Table 3. Intra- and interobserver variability

	COV, %	ICC	Bland-Altman	
			LOA	bias
Intraobserver variability				
RV LS	4	0.90	–3.6 to 4.1	0.2
LV LS	4	0.91	–3.0 to 2.6	–0.2
LV RS	15	0.97	–14.1 to 10.7	–1.7
LV CS	4	0.94	–2.6 to 2.6	–0.04
MD	8	0.98	–0.2 to 0.3	0.04
Interobserver variability				
RV LS	8	0.96	–2.8 to 2.3	–0.3
LV LS	4	0.95	–2.3 to 2.7	0.2
LV RS	17	0.96	–14.0 to 13.0	–0.4
LV CS	8	0.86	–3.6 to 4.4	0.4
MD	11	0.97	–0.4 to 0.3	–0.07

RV, right ventricle; LV, left ventricle; LS, longitudinal strain; CS, circumferential strain; RS, radial strain; MD, mechanical dispersion, standard deviation of time to peak strain in six ventricular segments; COV, coefficient of variation; ICC, interclass correlation coefficient; LOA, limits of agreement.

Discussion

This study investigated ventricular mechanics in newborn infants with CDH using STE. The principal findings were global bi-ventricular dysfunction, associated with ventricular interdependence and increased MD. These findings provide new insight into cardiac dysfunction in CDH and may have relevance for improving clinical management.

RV Dysfunction in CDH

We observed RV free wall and septal longitudinal dysfunction in CDH, the dominant direction of normal RV deformation, consistent with previous reports [13]. In adults with pulmonary arterial hypertension (PAH) similar patterns of impaired RV septal and free wall strain correlate with PAP, indicative of RV dysfunction secondary to increased afterload [3, 14]. In CDH, RV afterload is also persistently elevated due to structural abnormalities of the pulmonary vasculature [15]. However, we ob-

served no correlation between RV function and measures of PAP in the CDH group. This may be due to three factors: first, the practical challenge of accurately estimating PAP in infants; second, the normal physiological finding of elevated PAP in all infants in the first days of life [16], and third, the possibility that RV dysfunction in CDH may be secondary to mechanisms other than increased afterload.

LV Dysfunction in CDH

In CDH patients we observed impairment of longitudinal, circumferential, and radial LV function. Of note, both LV free wall and septal function were reduced. These findings add new insight to previous reports of LV dysfunction in CDH identified using tissue Doppler imaging [17]. Our findings suggest that LV dysfunction in CDH may be both secondary to RV dysfunction and primary in origin.

Ventricular Interdependence in CDH

Changes in structure or function in one ventricle may impact the other's performance due to shared myocardial fibres, septum, and enclosing pericardium [18]. We observed a correlation between LV and RV longitudinal systolic function in CDH cases indicating increased ventricular interdependence, as has previously been observed in children and adults with PAH [19].

In pulmonary hypertensive disease ventricular interdependence is considered to be a right-to-left phenomenon, with primary changes in RV structure and function leading to secondary changes in LV performance [20]. We observed evidence of this in CDH; an increased eccentricity index is an indication of RV dilatation and septal displacement, reducing LV size and impairing filling [21]. Furthermore, the reduction in LV septal strain in CDH may be secondary to increased right-sided septal wall stress impairing septal blood flow and function [22].

Mechanisms of Primary LV Dysfunction in CDH

The observed reductions in systolic strain in the free wall of the LV in CDH suggest that LV dysfunction may, in part, be independent of RV-mediated septal displacement or dysfunction.

Possible primary mechanisms of LV dysfunction in CDH include hypoplasia of the foetal LV, the acute increase in LV afterload during the transition from the foetal to postnatal environment, and hypoxia due to impaired oxygenation and intracardiac shunting [23].

Of note, strain is a measure of inherent myocardial function but may also demonstrate load dependency. Accordingly, LV strain alone cannot distinguish the relative contributions of these possible mechanisms to primary LV dysfunction.

Altered MD

Altered RV and LV MD has been observed in adults with PAH [11, 12, 24]. In CDH patients LV MD correlated with impaired LV LS in CDH, but not in controls. Whether increased MD is a contributing mechanism to impaired LV function, a secondary consequence, or a compensatory response merits further investigation.

Clinical and Therapeutic Significance

Our findings highlight the importance of routine clinical assessment of ventricular function in CDH, to appreciate the underlying pathophysiology in individual patients and guide targeted therapy. STE-derived strain may be an important new technique for routine clinical assessment of cardiac function in CDH. As we observed, STE is feasible in CDH with clinically acceptable image acquisition and analysis times, and importantly provides new insights into regional and global biventricular function and synchrony.

RV diastolic function has been previously demonstrated to correlate with clinical outcomes and the need for ECMO in CDH [25, 26]. Isolated RV dysfunction is a logical indication for afterload reduction using pulmonary vasodilators. However, in the presence of LV dysfunction pulmonary vasodilators may theoretically increase LV preload leading to worsening pulmonary venous hypertension [27]. Biventricular dysfunction may be better treated with direct cardiotropic support.

Ventricular interdependence and dyssynchrony may be important new therapeutic targets in CDH. Further studies are now indicated to understand the effects of existing cardiovascular therapies, including pulmonary vasodilators and inotropes, on these complex components of cardiac function, and to potentially identify new therapeutic approaches to optimise ventricular cross-talk and synchrony.

Limitations

This study used retrospective data. Some images were unsuitable for analysis, highlighting the challenge of echocardiography in CDH and the importance of optimal image acquisition for STE. Intra- and interobserver variability of STE-derived measures were similar to previous reports [7]. This is the first description of LV RS measurement in newborn infants and identified greater variability in this measure than other strain parameters.

Unfortunately, we did not have control data from healthy, disease-free infants collected at our institution for comparison with CDH cases. Instead we employed OA cases as controls, based on the fact that these cases were collected within the same time frame (<48 h of age), by the same study investigators, were demographically matched (including on gestational age), had normal cardiac anatomy, and were not receiving cardiorespiratory support. There are significant potential limitations of this group. It is feasible that they had some underlying cardiac dysfunction associated with their primary diagnosis. If dysfunction were present in the OA control group, however, this would likely have understated, rather than overstated, any observed difference between the OA and CDH groups.

The inclusion of existing published controls, of the same postnatal age as the CDH population, permitted the comparison of strain between CDH and healthy infants. However, these data originate from a different study centre and investigator group, which may have introduced interpopulation and additional observer variation.

The limited sample size highlighted the challenge of studying this rare condition, and the importance of validating these findings in larger studies. Non-invasive assessment of PAP in infants is challenging and prone to error, which may explain the lack of correlation with ventricular function in this study. We were unable to assess ventricular torsion or twist, due to insufficient apical views, and this is an important area for future investigation.

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Statement of Ethics

Study ethical approval was provided by the institutional Information Governance and Research Office.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors contributed to study design, data analysis and interpretation, drafting, and revision of this report. All authors have approved the final article.

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