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ORIGINAL INVESTIGATION

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Left ventricular rotational mechanics in infants with hypoxic ischemic encephalopathy and preterm infants at 36 weeks postmenstrual age: A comparison with healthy term controls

Colm R. Breatnach MB[1] | Eva Forman MB[1] | Adrienne Foran MD[1,2] | Cathy Monteith MB[3] | Lisa McSweeney MRes[3] | Fergal Malone MD[3] | Naomi McCallion MD[1,2] | Orla Franklin MD[4] | Afif El-Khuffash FRCPI MD DCE[1,2]

[1]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland

[2]Department of Paediatrics, School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

[3]Department of Obstetrics and Gynaecology, Royal College of Surgeons in Ireland, Dublin, Ireland

[4]Department of Cardiology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

Correspondence
Afif El-Khuffash, The Rotunda Hospital, Dublin, Ireland and Royal College of Surgeons in Ireland, Dublin, Ireland.
Email: afifelkhuffash@rcsi.ie

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Background and Aims: There is a paucity of data on left ventricle (LV) rotational physiology in neonates. We aimed to assess rotational mechanics in infants with hypoxic ischemic encephalopathy (HIE) and premature infants (<32 weeks) at 36 weeks postmenstrual age (PMA) (preterm group) and compare them with healthy term controls (term controls). We also compared the parameters in preterm infants with and without chronic lung disease (CLD).

Methods: Echocardiography was performed within 48 hours of birth or at 36 weeks PMA. LV basal and apical rotation, twist (and torsion=twist/LV length), twist rate (LVTR), and untwist rate (LVUTR) were measured. One-way ANOVA was used to compare values.

Results: There was no difference in gestation (40.0 [39.1–40.3] vs 39.9 [39.0–40.9], *P*>.05) or birthweight (3.7 [3.4–4.1] vs 3.5 [3.2–3.9], *P*>.05) between the HIE group (n=16) and term controls (n=30). The preterm group (n=35) had a gestation and weight of 36.0 [34.6–36.3] weeks and 2.3 [2.0–2.4] kg. The HIE group had lower twist, torsion, LVTR, and LVUTR than the other two groups. The preterm group had a more negative (clockwise) basal rotation while the term group had a more positive (counterclockwise) apical rotation. Preterm infants with CLD had higher apical rotation, twist, and torsion when compared to infants without CLD.

Conclusion: Infants with HIE have reduced rotational mechanics. Preterm infants at 36 weeks PMA have comparable measurements of twist to term infants. This is achieved by predominant basal rather than apical rotation. Infants with CLD have increased apical rotation.

KEYWORDS
echocardiography, left ventricular function, strain–strain rate, torsion

1 | INTRODUCTION

Left ventricular (LV) rotational mechanics describe the wringing motion (or twist) that occurs due to the rotation of the apex and base in opposite directions during systole, and the return to the baseline untwisted state during diastole.[1-3] The process is aided by the unique arrangement of the endocardial and epicardial fibers of the LV in a helical fashion (left-handed for epicardial and right-handed for endocardial fibers).[4,5] This wringing motion improves the ejection of blood from the LV during systole, and in early diastole, the recoil produced

by untwisting generates a suction force to facilitate diastolic filling.[6] Rotational mechanics can be assessed using two-dimensional speckle tracking echocardiography (2DSTE).[7] This technique has been validated against magnetic resonance imaging tissue tagging in the adult population,[8] and normative data for the pediatric and adult populations have been published.[9] Recently, our group have demonstrated that the serial measurement of rotational mechanics in the preterm neonatal population over the first week of age is feasible and reproducible.[10]

There remains a paucity of information on rotational mechanics in the neonatal population, particularly in important disease states. Chronic lung disease (CLD) is associated with maturational changes in the myocardium that to lead to altered right ventricular (RV) function; however, LV function is thought to be preserved.[11] The impact of CLD on rotational mechanics in preterm infants at 36 weeks postmenstrual age (PMA) is currently unknown. In addition, term infants with hypoxic ischemic encephalopathy (HIE) undergoing therapeutic hypothermia (TH) have reduced LV function measured using deformation,[12,13] and delineation of rotational mechanics in this population would be of interest. In this study, we aimed to assess LV systolic deformation parameters (strain and systolic strain rate) and rotational mechanics in healthy term infants during the early transitional period, infants with HIE undergoing TH, and preterm infants at 36 weeks PMA with and without CLD.

2 | METHODS

This was a cross-sectional study carried out in the neonatal intensive care unit (NICU) of the Rotunda Hospital, Dublin, Ireland, between July 2015 and June 2016. We recruited three groups: (1) normal healthy appropriately grown infants at term (defined as birth >37 weeks' gestation) born to mothers without significant maternal illness (diabetes of any type, preeclampsia, hypertension, clinical chorioamnionitis, or absent/reversed end-diastolic flow in the umbilical arteries anytime during the pregnancy); (2) infants with HIE (born with a pH <7.0 and a base excess >−16; Apgar score ≤5 at 10 minutes; need for resuscitation by 10 minutes of age; and clinical evidence of at least Sarnat grade 2 encephalopathy) treated with therapeutic hypothermia;[14] and (3) preterm infants born <32 weeks' gestation, surviving to 36 weeks PMA. We received ethical approval from the Hospital's Research Ethics Board, and informed consent from parents was obtained prior to enrollment. Infants were excluded if they had a suspected or definite chromosomal abnormality or congenital heart disease other than a patent ductus arteriosus (PDA) and a patent foramen ovale (PFO) identified antenatally or on the initial echocardiogram. We collected data on birth and neonatal characteristics including gestational age, the timing of the echocardiogram, birthweight, and Apgar scores at 5 minutes of age. Of note, none of the infants in the HIE group were in receipt of inotropes during the study period.

2.1 | Echocardiography

Echocardiography was performed using the Vivid S6 echocardiography system and 7-MHz multifrequency probe (GE Medical, Milwaukee, WI, USA) within the first 48 hours of life in the healthy term and HIE groups and at 36 weeks' corrected gestational age (or before hospital discharge) in the preterm group. All studies were conducted using a standardized functional protocol adapted from recently published guidelines.[15] The scans were stored as raw data in an archiving system (EchoPac, General Electric, version 112, revision 1.3; Milwaukee, WI, USA) and offline analysis was performed at a later date. Ejection fraction (EF) was measured using the Simpson's Biplane method. Left ventricular ejection time was obtained from a pulsed wave Doppler of the left ventricular outflow tract at the level of the aortic valve from the apical five-chamber view. Left ventricular output (LVO) was calculated as previously described.[16]

2.2 | Systolic deformation parameters and rotational mechanics

Left ventricle global longitudinal strain (LV GLS) and LV global systolic strain rate (SRs) were obtained using 2DSTE. Grayscale images of the LV from the apical four-, two-, and three-chamber views were obtained and a cine loop of three cardiac cycles was stored. The images were optimized to illustrate a clear endocardial and epicardial border of the LV walls without artifact, and a frame rate-to-heart rate ratio (FR:HR) between 0.7 and 0.9 was maintained as previously recommended.[17] A clear electrocardiogram signal was maintained during image acquisition. Offline measurement of LV GLS and SRs was conducted using dedicated software outlined above. A region of interest (ROI) was defined by tracing the endocardial border of the LV wall in the three views with the width set to match that of the wall. The software automatically tracked the movement of speckles within the walls to derive segmental GLS and SRs values. Values were only recorded if the software accepted the tracking and a visual inspection by operator confirmed adequate tracking. Global LV GLS and SRs values were obtained by averaging the results of the 18 segments of the three planes.

Rotational mechanics were derived by the same technique described above and by obtaining grayscale images of the LV from the parasternal short-axis views at the level of the mitral valve (to derive basal rotation) and at the level of the apex (to derive apical rotation). The same offline measurement principles were applied. Clockwise rotation was depicted as negative and anticlockwise rotation as positive. Twist was calculated as the difference between apical and basal rotation in degrees (°) using the following formula: Twist (°)=apical rotation (°) − Basal rotation (°). Torsion was derived by indexing twist to LV end-diastolic length (in cm) using the following formula: Torsion (°/cm)=LV Twist (°) ÷ LV length (cm). Indexing twist to LV length (torsion) enables comparison of twist across different LV lengths. Left ventricular twist rate (LVTR) is the speed at which the LV twists (degrees per second, °/s) during systole and LV untwist rate (LVUTR) is the speed at which the LV untwists (°/s) in early diastole (Figure 1, movie clip S1). All measurements were obtained from the analysis software.[10]

The feasibility and reproducibility of obtaining deformation and rotational measurements in the preterm and term populations were previously demonstrated by our group and others.[10,18-20] Strain measurements are highly reproducible with intra-class correlation

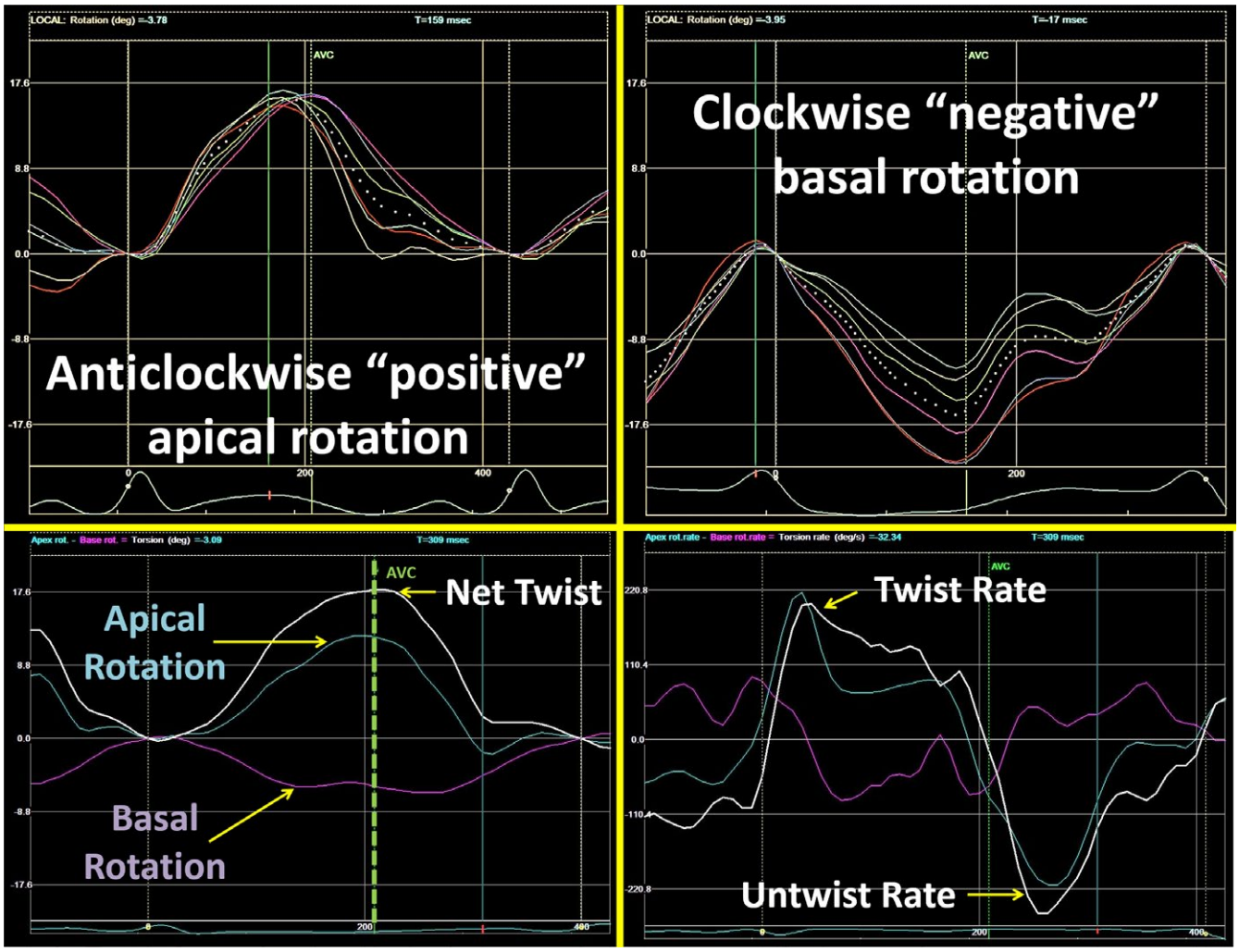

FIGURE 1 Measurement of rotational mechanics. The top panel demonstrates apical and basal rotation measured using dedicated software. Net twist is measured at the end of systole at aortic valve closure. The bottom panels demonstrate the measurement of twist, twist rate, and untwist rate (see movie clip S1 for imaging)

coefficients (ICCs) >.9 and coefficients of variation values <10%.[20] Recently, Nestaas et al.[21] demonstrated that the ICC for longitudinal peak systolic strain was .94/.87 inter/intra-observer and .91/.94 for peak systolic strain rate in analyses of left and right ventricles combined. Similarly, rotational mechanics are highly reproducible in neonates: basal and apical rotation, LV twist, and LV torsion demonstrate ICCs between from .78 and .96 (P<.001 for all). Intra- and inter-observer ICCs for LVTR and LVUTR range from .70 to .88 (P<.001 for all).[10]

2.3 | Statistical analysis

The cohort was divided into three groups: term control, preterm corrected, and term HIE. Continuous data were tested for normality using the Shapiro-Wilk test and a histogram representation of data. Data were summarized as means (standard deviation) or medians [interquartile range] as appropriate. Three-group analysis was conducted using one-way ANOVA or the Kruskal-Wallis one-way analysis of variance as appropriate. Pairwise analysis between the groups was conducted using the Bonferroni adjustment. Two-group analysis was conducted using the independent t test or the Mann-Whitney U test as appropriate. Linear regression was used to assess the independent effect of important variables on the functional parameters. The independent effect of the group and HR on SRs, LVTR, and LVUTR was assessed. SPSS (IBM, Armonk, NY, USA; version 23) was used to conduct the analysis, and we accepted a P value <.05 as appropriate.

3 | RESULTS

3.1 | Study groups and conventional LV functional parameters

Eighty-one infants were included in the study: 30 controls, 35 preterm corrected infants, and 16 infants with HIE. Table 1 illustrates their gestation and weight at the time of scanning, in addition to the conventional functional measurements. There was no difference in the gestation, time of scan, or weights between term control and term HIE groups (Table 1). Preterm infants were of a lower gestation and a

TABLE 1 Patient demographics and conventional left ventricular functional parameters

	Term control n=30	Preterm corrected n=35	Term HIE n=16	*P*
Time of scan (hours of age)	26 [13-42]	NA	23 [13-30]	.4
Gestation at scan (wk)	39.9 [39.0-40.9]*	36.0 [34.6-36.3]‡	40.0 [39.1-40.3]	<.001
Weight (kg)	3.5 [3.2-3.9]*	2.3 [2.0-2.4]‡	3.7 [3.4-4.1]	<.001
Heart rate	119 (13)*,†	155 (16)‡	97 (13)	<.001
LVET (ms)	204 (17)*,†	184 (20)‡	240 (23)	<.001
Ejection fraction (%)	60 (6)	60 (6)	57 (6)	.07
LVO (mL/kg/min)	136 (28)*,†	212 (41)‡	93 (33)	<.001

Values were presented as means (standard deviation) or median [interquartile range]. One-way ANOVA was used to assess differences between the three groups. Pairwise comparisons were conducted using the Bonferroni adjustment. LVET, left ventricular ejection time; LVO, left ventricular output; HIE, hypoxic ischemic encephalopathy.

*P value <.05 between term control and preterm corrected.

†P value <.05 between term control and term HIE.

‡P value <.05 between preterm corrected and term HIE.

lower weight at the time of the scan (Table 1). Heart rate was different between all three groups with the highest HR in the preterm group and the lowest in the term HIE group. LVO values followed a similar pattern (Table 1).

3.2 | Deformation and rotational mechanics in the three groups

Table 2 illustrates LV GLS, LV systolic SR in addition to LV rotational mechanics in the three groups. Median FR:HR ratio was within the recommended range. Term controls had the highest GLS, while term HIE had the lowest (Table 2). Term controls and preterm corrected infants had similar systolic SR, both of which were higher than term HIE infants. Preterm infants had the highest systolic torsion values, while term HIE exhibited the lowest values. In the preterm group, twist was achieved by a more pronounced negative basal rotation, while in term controls twist was achieved by a more pronounced positive apical rotation. Term HIE infants had the lowest apical and basal rotations when compared to the two other groups (Table 2).

The same pattern was noted for LVTR and LVUTR: Preterm infants had the highest values when compared to the two other groups, while term HIE had the lowest values (Table 2, Figure 2). The association between the groups and systolic SR remained significant when adjusting for HR on linear regression (Group standardized β −0.25, P=.008; HR standardized β 0.55, P<.001). Similarly, the association between the group and LVUTR remained significant when adjusting for HR on linear regression (Group standardized β −0.23, P=.02; HR standardized β 0.40, P<.001). When adjusting for HR, the relationship between group and LVTR was no longer significant (Group standardized β −0.08, P=.37; HR standardized β 0.54, P<.001).

TABLE 2 Systolic deformation and rotational mechanics in the three groups

	Term control n=30	Preterm corrected n=35	Term HIE n=16	*P*
FR-to-HR ratio	0.8 [0.7 to 0.9]†	0.8 [0.7 to 0.8]‡	0.9 [0.8 to 1.0]	<.001
LV GLS (%)	−24.9 (2.7)*,†	−22.9 (2.6)‡	−19.5 (3.7)	<.001
LV systolic SR (1/s)	−2.0 (0.3)†	−2.2 (0.4)‡	−1.5 (0.3)	<.001
Apical rotation (°)	17.0 (5.0)*,†	13.0 (5.9)	12.0 (5.1)	<.001
Basal rotation (°)	1.0 (4.1)*	−6.6 (3.9)‡	0.2 (3.4)	<.001
LV twist (°)	15.8 (6.5)†	18.6 (5.0)‡	11.0 (5.9)	<.001
LV torsion (°/cm)	5.7 (2.4)*,†	7.3 (2.1)‡	3.9 (2.1)	<.001
LV twist rate (°/s)	134 [119 to 155]*,†	186 [151 to 224]‡	107 [69 to 135]	<.001
LV untwist rate (°/s)	−192 [−160 to −228]†	−223 [−144 to −296]‡	−127 [−102 to −147]	<.001

Values were presented as means (standard deviation) or median [interquartile range]. One-way ANOVA was used to assess differences between the three groups. Pairwise comparisons were conducted using the Bonferroni adjustment. FR to HR, frame rate to heart rate; LV, left ventricle; GLS, global longitudinal strain; SR, strain rate; HIE, hypoxic ischemic encephalopathy.

*P value <.05 between term control and preterm corrected.

†P value <.05 between term control and term HIE.

‡P value <.05 between preterm corrected and term HIE.

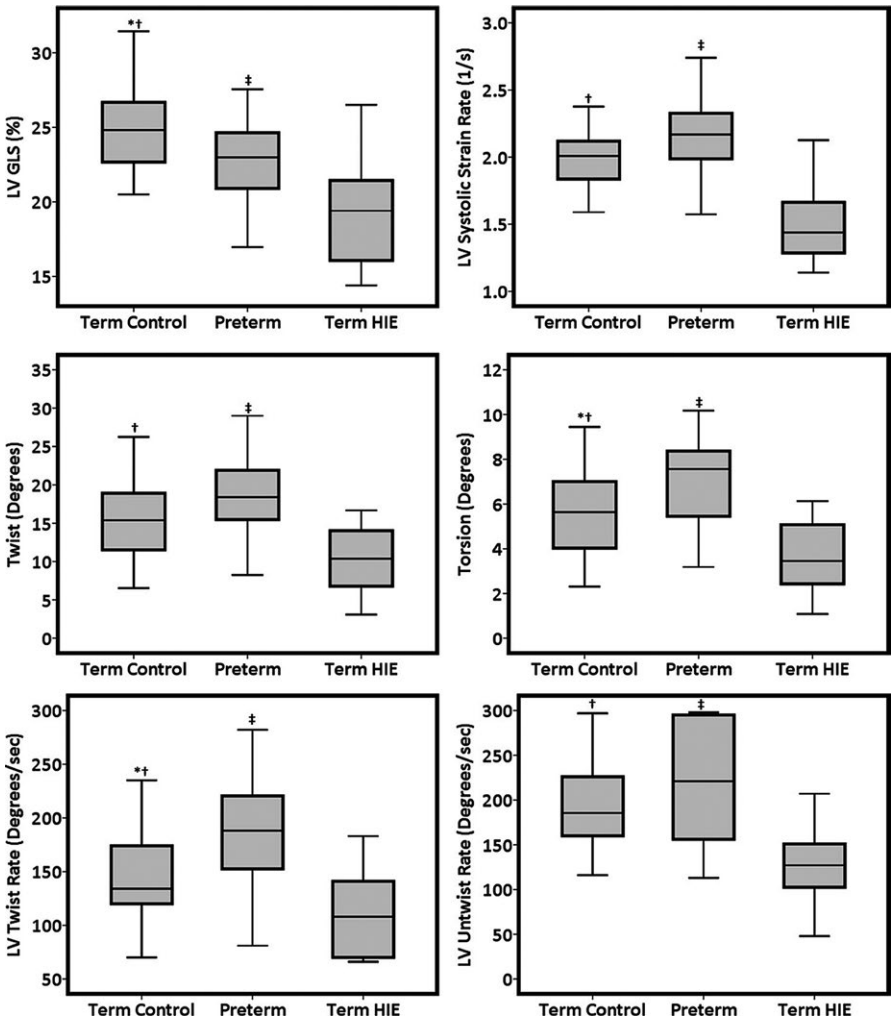

FIGURE 2 Deformation and rotational parameters in the three groups. LV=left ventricle; GLS=global longitudinal strain. One-way ANOVA was used to assess differences between the three groups. Pairwise comparisons were conducted using the Bonferroni adjustment. **P* value <.05 between term control and preterm corrected. †*P* value <.05 between term control and term hypoxic ischemic encephalopathy (HIE). ‡*P* value <.05 between preterm corrected and term HIE

3.3 | The effect of chronic lung disease in preterm infants

The preterm group had a median gestation and weight at birth of 28.0 weeks [26-30] and 1100 g [750-1360]. Twelve infants (34%) developed CLD at 36 weeks PMA. Infants with CLD had a lower gestation (25.6 [24.7-27.2] vs 29.7 [27.9-31.0] weeks, *P*<.001) and birthweight (665 [600-920] vs 1220 [1100-1580] g, *P*<.001). There was no difference in HR, EF, LVO, LV GLS, or LV systolic SR between the two groups (Table 3). Preterm infants with CLD had a higher (more positive) apical rotation and a higher LV twist and torsion. Basal rotation, LVTR, and LUVTR were not different between the two groups (Table 3). The association between CLD and apical rotation remained significant when adjusting for gestation (β=6.2, *P*=.01). The association between CLD and twist (β=3.7, *P*=.08) and between CLD and torsion (β=1.6, *P*=.08) became a trend when adjusted for gestation.

TABLE 3 Deformation and rotational mechanics in preterm infants with and without chronic lung disease (CLD)

	No CLD n=23	CLD n=12	*P*
Heart rate	156 (12)	154 (22)	.77
Ejection fraction (%)	61 (6)	57 (6)	.09
LVO (mL/kg/min)	215 (44)	208 (39)	.69
LV GLS (%)	−23.1 (2.6)	22.3 (2.7)	.35
LV systolic SR (1/s)	−2.3 (0.5)	−2.1 (0.2)	.24
Apical rotation (°)	10.7 (5.0)	17.5 (4.7)	<.001
Basal rotation (°)	−7.6 (3.6)	−4.9 (4.2)	.06
LV twist (°)	17.1 (4.8)	21.6 (3.8)	.009
LV torsion (°/cm)	6.7 (2.2)	8.4 (1.5)	.02
LV twist rate (°/s)	183 [147 to 218]	208 [166 to 228]	.20
LV untwist rate (°/s)	−187 [−134 to −295]	−243 [−185 to −295]	.21

Values were presented as means (standard deviation) or median [interquartile range]. LVO, left ventricular output; LV, left ventricle; GLS, global longitudinal strain; SR, strain rate.

4 | DISCUSSION

The study of LV rotational mechanics and torsional deformation offers a novel insight into LV myocardial function, and possibly, its ability

to adapt different physiological and maturational environments. Our study demonstrated significant differences in deformation and rotational mechanics patterns among the three groups. LV twist is increasingly recognized as an important determinant of effective and efficient systolic performance. The wringing motion of the LV supplements the deformation occurring in the longitudinal, radial, and circumferential planes to facilitate an increase in intra-cavity pressure and ejection of blood. The rapid untwisting which follows during early diastole (and during isovolumic relaxation) results in a quick decrease in LV cavity pressure to create a pressure gradient between the left atrium and LV. This significantly contributes to early diastolic suction and LV filling.[3,22]

Apical rotation remains constantly positive (anticlockwise) with advancing age. Basal rotation, however, gradually changes from being positive (anticlockwise) in infancy to being negative (clockwise) in adulthood. Consequently, the LV rotational motion changes from a full rotation (both apex and base moving in the same direction) to a wringing motion (apex and base move in opposing directions).[9,23] This gradual change can be explained by gradual subendocardial fibrosis occurring with advancing age leaving the subepicardial movement unopposed thereby facilitating the wringing motion. Twist is determined by the interaction of subepicardial fibres (promoting torsion) and subendocardial fibers (inhibiting torsion),[24] so dysfunction in the endocardial layer leads to a stronger positive clockwise twist. In addition, this increase in torsional function is thought to be a compensatory mechanism for the reduction in "conventional" LV function and the stiffening of the myocardium associated with advancing age.[9] The values obtained from the healthy term control group in our study are consistent with the literature. The unique pattern of apical and basal rotation, and the resultant twist/torsion in the two studied disease states when there is a relative lack of difference in conventional measurements (such as EF) suggest that those functional parameters are sensitive markers of function in differing physiological environments.

4.1 | Infants with hypoxic ischemic encephalopathy

Infants who suffer an asphyxial and ischemic insult will usually have multiorgan involvement which includes the heart. This ischemic damage can manifest as a reduction in systolic and diastolic function in addition to a fall in cardiac output. In addition, the provision of therapeutic hypothermia to this population to facilitate the recovery of the brain and limit reperfusion injury can add additional stressors on the already damaged myocardial tissue. This includes a reduction in the basal metabolic rate and an increase in systemic vascular resistance. Increased afterload appears to decrease LV twist and untwist rates in adults[25] and in the preterm neonatal population.[26] Therefore, it is highly likely that there is inherent myocardial damage in addition to an unfavorable physiological environment associated with HIE. Several studies have demonstrated reduced LV strain and systolic strain rate in HIE infants both with and without therapeutic hypothermia when compared with term controls.[12] The magnitude of LV dysfunction measured using deformation can also predict mortality in this population.[13] In our study, term HIE infants did have lower LV GLS and SRs (although not to same extent demonstrated in other studies). More importantly, we demonstrated significantly depressed rotational mechanics in this population manifest by lower apical rotation, a lack of basal rotation movement, and reduced LVTR and LVUTR. The finding cannot be attributed to differences in HR observed between the groups as systolic SR and LVUTR remained significantly dependent on group allocation. The lack of expected adaptation to reduced longitudinal LV function observed in adults (and preterm infants, see below) suggests direct myocardial damage. This pattern is also observed in children with leukemia treated with anthracycline which is known to have significant cardiotoxic effects.[27]

4.2 | Preterm infants at 36 weeks PMA

Infants in the preterm corrected group demonstrated higher LV torsion when compared with the term control group. This higher torsion was achieved by a more pronounced negative (clockwise) basal rotation. The higher torsion in this population was also associated with higher LVTR and LVUTR. We previously demonstrated an accelerated change in basal rotation pattern in the extremely low birthweight population (from positive anticlockwise to a negative clockwise) which mimics the change seen occurring into adulthood. This change occurred within the first week of age.[10] The persistence of this negative basal rotation pattern in preterm infants to term corrected seen in our study highlights the difference in the myofibril architecture of preterm infants. The counterclockwise basal rotation in healthy term infants has been attributed to either fundamental changes in the cardiac structure or the length over which angulated epicardial fibres act[28] which increases with growth. This is not the case in preterm infants, in whom cardiac structure seems to more closely mimic that of the elderly population. This may represent an accelerated subendocardial fibrosis pattern as a result of preterm birth. This unique pattern of rotational mechanics seen in the preterm population may act as a compensatory mechanism for reduced LV function secondary to the unique architecture of preterm infants which is characterized by an inefficient contractile function and increased stiffness.[29] The lower LVTR and LVUTR described in children compared with adults during exercise are considered to be caused by the higher intrinsic relaxation properties of the pediatric heart.[30] Conversely, diastolic impairment, as seen in preterm infants, would lead to an increase in twist and untwist rates as seen here and in previous studies.[31]

4.3 | The impact of chronic lung disease on rotational mechanics

Preterm corrected infants with CLD had a significantly higher LV twist and torsion secondary to higher (more positive) apical rotation. Those differences occurred despite similar longitudinal deformation parameters between the two groups. Several studies have previously postulated that LV function remains preserved in preterm infants with CLD when measured at 36 weeks PMA.[11,32] The difference observed in our study suggests that rotational mechanics may be very sensitive measures of LV function and may act as a compensatory mechanism to reduced longitudinal function.

4.4 | Limitations of the study

Echocardiography was performed at single time points for each of the patient groups, so we were unable to examine trends over time which may yield valuable information. The studied numbers are small for each group, and as a result, this precluded us from assessing the impact of various other perinatal variables. Larger studies are needed to support our findings.

5 | CONCLUSION

The clinical utility of LV rotational mechanics in the neonatal population is slowly emerging. Those techniques may offer novel insights into LV function in the normal neonatal population and those with different disease states. Infants with HIE have a global decrease in both deformation and rotational mechanics likely due to a combination of cardiac ischemic dysfunction and the impact of cooling. Twist in preterm infants at 36 weeks' corrected gestation is more dependent on basal rotation than the apical driven twist of healthy term controls. This study provides further information to the field of neonatal echocardiography, adding to our understanding on deformation and rotational mechanics in different neonatal populations.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Movie clip S1 Basal rotation usually occurs in a clockwise fashion (depicted as a negative rotation). Apical rotation usually occurs in an anticlockwise fashion (depicted as a positive rotation). Speckle tracking echocardiography can be used to measure rotation and the resultant twist.

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