Assessment of myocardial function in preterm infants with chronic lung disease using tissue doppler imaging

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Title: Assessment of Myocardial Function in Preterm Infants with Chronic Lung Disease using Tissue Doppler Imaging

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ABSTRACT:

Objectives: To assess myocardial function and presence of pulmonary hypertension (PH) using both tissue Doppler imaging (TDI) and conventional echocardiography in preterm infants <32weeks gestation with chronic lung disease (CLD).

Design: Prospective observational study.

Setting: Tertiary neonatal intensive care unit.

Patients: Three groups of preterm infants were recruited. Group 1 - CLD receiving positive pressure airway support [including high-flow humidified nasal cannula oxygen] (n=25). Group 2 - CLD receiving low-flow nasal oxygen (n=25) and group 3 no CLD (n=22).

Methods: Echocardiography was performed around 36 weeks corrected gestational age. Myocardial function and PH were assessed using both conventional (left ventricular fractional shortening [LVFS] and left ventricular output [LVO], tricuspid regurgitation and ventricular septal flattening) and TDI techniques (myocardial velocities, myocardial performance index [MPI] and right ventricular isovolumetric relaxation time [RV-IVRT]).

Results: The MPI of right (RV) and left (LV) ventricles was significantly higher in CLD infants: mean RV MPI group 1 – 0.79, group 2 – 0.65 and group3 – 0.52. LV MPI: group 1 – 0.77, group 2 – 0.70 and group 3 – 0.45. There was a trend towards higher MPIs in group 1 compared to group 2. LVFS and LVO were similar across all three groups.

RV-IVRT was also significantly higher in infants with CLD infants (group 1 – 0.06 seconds, group 2 – 0.06 seconds and group 3 – 0.05 seconds). PH was not detected by conventional echocardiography.

Conclusion: Infants with CLD have evidence of relative biventricular dysfunction and higher pulmonary arterial blood pressure as demonstrated by TDI which were not detected by conventional echocardiography.

INTRODUCTION:

Chronic lung disease of prematurity (CLD) - defined as a persisting need for respiratory support and/or supplemental oxygen at 36 weeks corrected gestational age (CGA) - is the commonest respiratory disease in infancy (1). CLD usually occurs in infants born at <32 weeks gestational age (GA) and can lead to persisting abnormalities of lung function through to adolescence.(1,2,3) Although most complications of CLD are respiratory, cardiovascular complications such as pulmonary hypertension (PH) (4,5) and myocardial dysfunction(6,7,8) are well recognised. CLD is the commonest respiratory cause of PH in children(9) and although the precise incidence in CLD is not known, single centre studies report PH in 20-37% of preterm babies (<32weeks GA).(9-11) Cardiac catheterisation remains the gold standard for diagnosing PH in children,(9) however, conventional echocardiographic measures such as tricuspid regurgitation velocity (TR) are widely used to try to identify PH in the neonatal period(5) but the accuracy of TR in this respect is uncertain.

Tissue Doppler imaging (TDI) is a validated echocardiographic technique for evaluating myocardial function in preterm infants.(12-14) By analysing the Doppler signals from the myocardium, systolic and diastolic velocities representing relative myocardial function can be measured (low myocardial velocities indicating myocardial dysfunction). Myocardial performance index (MPI), a measure of systolic and diastolic myocardial function is also calculated (a higher MPI indicating myocardial dysfunction). Pulmonary arterial blood pressure can also be assessed indirectly using TDI by measuring right ventricular isovolumetric relaxation time (RV-IVRT: with a longer RV-IVRT indicating higher pulmonary blood pressure).(6, 15-18)

Previous reports of TDI in the assessment of myocardial function in preterm infants with CLD prior to discharge are limited to one small study (21 infants) and a case report.(6,7)

The aims of this study were (i) to evaluate myocardial function in preterm infants (<32weeks GA) diagnosed with CLD using both TDI and conventional echocardiographic assessment of left ventricular function (fractional shortening [LVFS] and left ventricular output [LVO]), and (ii) to assess the presence of pulmonary hypertension (PH) using conventional echocardiographic measures (tricuspid regurgitation [TR] and ventricular septal flattening) and TDI-derived RV-IVRT.

METHODS:

All preterm infants (<32 weeks GA) on the tertiary neonatal unit at Birmingham Women's Hospital were eligible for inclusion. CLD was defined as persisting need for respiratory support and / or supplemental oxygen in preterm infants at 36 weeks CGA. Infants with CLD were classified into 2 groups based on the level of respiratory support - group 1: infants with CLD needing positive airway pressure support (CPAP, biphasic CPAP (BiPAP) and High-flow humidified nasal oxygen), group 2 included infants with CLD needing low-flow nasal oxygen. Group 3 included preterm infants without CLD (controls). Infants with major congenital malformations including congenital heart defects were excluded. Ethical approval, institutional research and development approval and written informed parental consent were obtained prior to recruitment.

A single echocardiogram was performed by the same investigator (PKY) on all infants between 36^{+0} and 37^{+2} weeks CGA using a Philips HD11xe ultrasound system with a S12-4MHz transducer (Philips Healthcare, Best, The Netherlands).

Conventional echocardiographic assessment:

Normal cardiac anatomy was ascertained and the presence or absence of a PDA was determined using a modified high parasternal long axis view (ductal view) and colour flow Doppler. M-mode echocardiography was used to calculate LVFS using a parasternal long-axis view at the level just distal to the mitral valve leaflets.(19) LVO was calculated using previously described technique.(20) Conventional echocardiographic assessment of PH using tricuspid regurgitation (TR) jet and ventricular septal flattening was undertaken. TR was used as a screening tool and was classified as mild (<2m/s), moderate (2 – 2.8m/s) and severe (>2.8m/s). (9) Infants with severe TR and/or septal flattening were to be referred to paediatric cardiologists for further assessment of elevated pulmonary blood pressure.

Tissue Doppler imaging:

Myocardial velocities were obtained from an apical four-chamber view. A Pulse Wave Doppler sample gate of 0.12cm was used and an angle of insonation of <20º was maintained using 2D hold; the Doppler signal was not corrected. Myocardial velocity signals were recorded from the medial mitral (MMA) and lateral mitral (LMA) annuli representing left ventricular (LV) function and from the lateral tricuspid annulus (LTA) representing right ventricular (RV) function. Peak systolic (S'), early diastolic (E') and late diastolic (A') myocardial velocities were measured (figure 1). MPI was calculated using the TDI wave forms as previously described.(21) RV-IVRT - the time interval between the end of systole and the beginning of diastole - was also measured (see figure 1). Offline analysis was performed for all measurements on the same ultrasound system and average measurements over 2-3 cardiac cycles were used.

Routine clinical data, including level of respiratory support at the time of investigation were also collected (table 1)

Table 1: Clinical characteristics of infants in groups 1, 2 and 3

Clinical characteristic	**Group 1**	**Group 2**	**Group 3**	***p* value**	**Pair wise comparisons [(*)] *p* value**		
	***n* = 25**	***n* = 25**	***n* = 22**		**1 vs. 2**	**2 vs. 3**	**1 vs. 3**
Gestational age wks. mean (SD)	27.0 (1.9)	27.2 (1.9)	28.6 (2.3)	0.021[(a)]	NS	NS	0.028
Birth weight gm median (range)	778 (500 - 1640)	860 (500 - 1790)	1030 (570 - 1700)	0.040[(b)]	NS	NS	0.023
Ventilation days median (range)	79 (44 - 125)	35 (4 - 89)	10 (1 - 64)	<0.001[(b)]	<0.001	<0.001	<0.001
Antenatal steroids *n* (%)	19 (76.0)	17 (68.0)	16 (72.7)	NS[(c)]	-	-	-
Exogenous surfactant *n* (%)	24 (96.0)	21 (84.0)	10 (45.5)	<0.001[(c)]	NS	0.008	0.002
Pharmacological treatment for PDA *n*(%)	10 (40.0)	8 (32.0)	2 (9.1)	NS[(c)]	-	-	-
Surgical ligation of PDA *n* (%)	9 (36.0)	2 (8.0)	0 (0)	0.014[(c)]	0.051	NS	0.006
Postnatal Dexamethasone *n* (%)	13 (52.0)	1 (4.0)	0 (0)	<0.001[(c)]	<0.001	NS	<0.001
Supplemental oxygen at discharge *n* (%)	17 (68.0)	13 (52.0)	0 (0)	<0.001[(c)]	NS	<0.001	<0.001

[(a)] ANOVA test followed by Bonferroni multiple comparison tests[(b)] Kruskall Wallis rank test followed by Mann-Whitney U pairwise tests. p-values have been multiplied by three
[(c)] Pearson Chi-squared test
NS - not significant

STATISTICAL ANALYSES:

Normally distributed data are presented as Mean and SD and skewed data are presented as medians and ranges. Statistical analyses were performed using SPSS v20 (SPSS, Chicago, IL). The Shapiro-Wilk test was used to test the normality of the data. ANOVA or Kruskal-Wallis tests were used for comparisons involving three or more groups, depending on data distributions. When the analysis showed a significant result, we performed post-hoc

multiple comparison test accounting adequately for the type I error inflation. We have used Bonferroni multiple range test after a significant ANOVA or multiple pairwise Mann Whitney U tests after a significant Kruskal-Wallis. In the latter case, we adjusted significance level to account for multiplicity of tests and accordingly, we multiplied pairwise comparison p-values by the number of tests performed. T - Student test and Mann-Whitney U test were used to test significance of normal and skewed data respectively where appropriate. Chi-squared test was used to compare categorical data. A *p* value of <0.05 was considered significant. The inter- and intra-observer reliability of TDI measurements have been previously established by our group and other investigators.(12-14, 22-24) Conventional echocardiographic and TDI measurement, if considered normal distributions, were compared after adjusting for gestational age and birth weight using a generalized linear regression model. We checked if adding these two confounders to the linear model changed the estimations of the differences between groups.

RESULTS

Seventy two preterm infants, <32 weeks GA, were recruited into the three groups. Group 1 had 25 infants, group 2 - 25 infants and group 3 - 22 infants.(Table 1).

Conventional echocardiographic assessment

No significant structural heart defect was found in any infants. According to previously published criteria,(25) only one infant (in group 1) had a haemodynamically significant PDA. None had echocardiographic evidence of elevated pulmonary blood pressure (severe TR and/or ventricular septal flattening) requiring further cardiology assessment. Five infants had moderate TR (2 each in groups 1 and 2 and 1 in group 3). The remaining 67 infants

either had mild or no TR. LVFS and LVO did not differ significantly between the three groups (table 2).

Table 2: Conventional echocardiographic and TDI measurements of cases and controls

Clinical characteristic		Group 1	Group 2	Group 3	*p* value	Pair wise comparisons *p* value		
		***n* = 25**	***n* = 25**	***n* = 22**		**1 vs. 2**	**2 vs. 3**	**1 vs. 3**
LVFS (%)		31.3 (7.04)	35.56 (9.11)	31.89 (7.79)	NS[(b)]	-	-	-
LVO (ml/kg/min)		396 (88)	383(67)	400(89)	NS[(b)]	-	-	-
MMA	**S' (cm/s)**	5.45 (0.93)	5.09 (0.88)	4.92 (0.68)	NS[(b)]	-	-	-
	E' (cm/s)	5.42 (1.43)	6.21 (1.40)	5.80 (0.78)	NS[(b)]	-	-	-
	A' (cm/s)	7.89 (1.79)	7.64 (1.55)	7.39 (1.75)	NS[(a)]	-	-	-
	MPI	0.74 (0.16)	0.65 (0.19)	0.47 (0.12)	<0.001[(b)]	0.024	<0.001	<0.001
LMA	**S' (cm/s)**	5.84 (0.61)	5.50 (0.87)	5.39 (0.93)	NS[(a)]	-	-	-
	E' (cm/s)	6.16 (1.24)	6.97 (1.41)	7.00 (1.11)	NS[(b)]	-	-	-
	A' (cm/s)	9.26 (2.15)	8.45 (1.46)	9.32 (2.24)	NS[(a)]	-	-	-
	MPI [(*)]	0.77 (0.14)	0.70 (0.20)	0.45 (0.14)	<0.001[(a)]	NS	<0.001	<0.001
LTA	**S' (cm/s)**	10.06 (2.32)	9.00 (1.31)	8.46 (1.06)	0.026[(b)]	NS	NS	0.009
	E' (cm/s)	10.03 (1.48)	9.09 (1.82)	8.89 (1.57)	NS[(a)]	-	-	-
	A' (cm/s)	12.02 (2.43)	12.28 (1.9)	11.95 (2.96)	NS[(a)]	-	-	-
	MPI	0.79 (0.33)	0.65 (0.17)	0.52 (0.17)	< 0.001[(b)]	NS	0.006	<0.001
	IVRT (sec)*	0.06 (0.02)	0.06 (0.01)	0.05 (0.01)	0.001[(a)]	NS	0.031	0.001

[(a)] ANOVA test
[(b)] Kruskall Wallis rank test
[(*)] Remains still significant after adjusting for GA and BW
NS - not significant; LVFS - left ventricular fractional shortening; LVO - left ventricular output; MMA - medial mitral annulus; LMA - lateral mitral annulus; LTA - lateral tricuspid annulus; IVRT - isovolumetric relaxation time; S' - peak systolic velocity; E' - early diastolic velocity; A' - late diastolic velocity; MPI - myocardial performance index.

Tissue Doppler assessment

Infants with CLD (groups 1 and 2) had significantly higher MPIs at all three sites and longer RV-IVRT compared to infants without CLD (group 3) [table 2]. Infants in group 1 had higher MPI compared to group 2 only at the MMA. There was no statistically significant difference in myocardial velocities, LMA and LTA MPIs and the RV-IVRT between groups 1 and 2 (table 2).

Sub-group analysis:

We performed the following sub-group analyses among infants with CLD (groups 1 and 2): i) infants who received postnatal dexamethasone for the management of CLD (according to DART protocol) (26) were compared to those who did not, and (ii) infants discharged on supplemental oxygen were compared to infants breathing room air at discharge.

Fourteen of the 50 infants with CLD received postnatal dexamethasone. Myocardial function assessments in these infants are shown in table 3. Infants who required dexamethasone had significantly higher MPIs at all three sites compared to infants who did not. No infant had evidence of ventricular hypertrophy as assessed subjectively in the parasternal long axis view.

Table 3: Sub-group analysis: Conventional echocardiographic and TDI measurements of infants with CLD who received postnatal dexamethasone vs. no dexamethasone

Clinical characteristic		Desamethasone *n* = 14	No Dexamethasone *n* = 36	*p* value
LVFS (%)		32.2 (7.3)	33.3 (8.6)	NS[(a)]
LVO (ml/kg/min)		401(76)	380 (73)	NS[(a)]
MMA	**S' (cm/s)**	5.52 (1.11)	5.17 (0.83)	NS[(b)]
	E' (cm/s)	5.15 (1.06)	6.04 (1.52)	NS[(a)]
	A' (cm/s)	7.71 (1.95)	7.80 (1.58)	NS[(a)]
	MPI	0.78 (0.18)	0.66 (0.17)	<0,001[(b)]
LMA	**S' (cm/s)**	5.82 (0.66)	5.61 (0.81)	NS[(a)]
	E' (cm/s)	6.06 (1.59)	6.72 (1.29)	NS[(b)]
	A' (cm/s)	8.62 (1.96)	8.93 (1.86)	NS[(a)]
	MPI	0.80 (0.14)	0.71 (0.18)	<0.001[(b)]
LTA	**S' (cm/s)**	9.75 (2.20)	9.44 (1.85)	NS[(b)]
	E' (cm/s)	9.62 (1.66)	9.49 (1.76)	NS[(a)]
	A' (cm/s)	12.06 (2.48)	12.19 (2.06)	NS[(a)]
	MPI	0.83 (0.39)	0.67 (0.19)	0.015[(b)]
	IVRT (sec)	0.06 (0.02)	0.06 (0.01)	NS[(b)]

[(a)] T-student test
[(b)] Mann-Whitney U test
NS - not significant; LVFS - left ventricular fractional shortening; LVO - left ventricular output; MMA - medial mitral annulus; LMA - lateral mitral annulus; LTA - lateral tricuspid annulus; IVRT - isovolumetric relaxation time; S' - peak systolic velocity; E' - early diastolic velocity; A' - late diastolic velocity; MPI - myocardial performance index

Thirty out of the 50 infants with CLD were discharged on supplemental oxygen. Myocardial function in these infants is shown in table 4. Those discharged on supplemental oxygen had significantly higher MPIs at all three sites, higher peak systolic velocities at MMA and LTA

and lower early diastolic velocity at LMA compared to those infants who did not require supplemental oxygen at discharge.

Table 4: Sub-group analysis: Conventional echocardiographic and TDI measurements of infants with CLD discharged on supplemental oxygen vs. no supplemental oxygen at discharge

Clinical characteristic		**Oxygen at discharge**	**No Oxygen at discharge**	***p* value**
		***n* = 30**	***n* = 20**	
LVFS (%)		33.8 (9.1)	31.9 (7.0)	NS[(a)]
LVO (ml/kg/min)		426 (78)	392 (63)	NS[(b)]
MMA	**S' (cm/s)**	5.45 (1.00)	4.99 (0.71)	0,026[(b)]
	E' (cm/s)	5.87 (1.63)	5.70 (1.24)	NS[(a)]
	A' (cm/s)	8.09 (1.96)	7.39 (1.15)	NS[(a)]
	MPI	0.71 (0.19)	0.66 (0.15)	<0.001[(b)]
LMA	**S' (cm/s)**	5.58 (0.79)	5.80 (0.73)	NS[(a)]
	E' (cm/s)	6.24 (1.22)	7.06 (1.47)	0.020[(a)]
	A' (cm/s)	8.83 (1.68)	8.89 (2.17)	NS[(a)]
	MPI	0.76 (0.15)	0.70 (0.20)	<0.001[(a)]
LTA	**S' (cm/s)**	9.63 (1.79)	9.38 (2.17)	0.030[(b)]
	E' (cm/s)	9.59 (1.50)	9.41 (2.08)	NS[(a)]
	A' (cm/s)	12.36 (2.16)	11.82 (2.12)	NS[(a)]
	MPI	0.75 (0.30)	0.67 (0.20)	0.004[(b)]
	IVRT (sec)	0.06 (0.01)	0.06 (0.01)	NS[(a)]

[(a)] T-student test
[(b)] Mann-Whitney U test
NS - not significant; LVFS - left ventricular fractional shortening; LVO - left ventricular output; MMA - medial mitral annulus; LMA - lateral mitral annulus; LTA - lateral tricuspid annulus; IVRT - isovolumetric relaxation time; S' - peak systolic velocity; E' - early diastolic velocity; A' - late diastolic velocity; MPI - myocardial performance index

DISCUSSION:

We have used both conventional and TDI echocardiographic assessments to evaluate myocardial function in infants with CLD. To our knowledge, only one small study, involving 21 preterm infants, has been previously published.(6) In the current study we have demonstrated that biventricular MPIs were significantly higher in preterm infants with CLD at 36 weeks CGA compared to those without CLD - indicating relative myocardial dysfunction. RV-IVRT measured using TDI was longer in CLD infants compared to those without CLD indicating higher pulmonary arterial pressure. However, conventional echocardiographic assessments of LV function were similar.

M-mode derived LVFS is an unreliable method of assessing LV systolic function due to the differences in ventricular geometry (in neonates compared to adults) and non-homogeneity of LV wall motion.(27) A recent study in preterm infants born at <29 weeks gestation has also demonstrated that LVFS is unreliable during the transitional period.(28) Similarly LVO measurements in preterm neonates are affected by the patent fetal shunts, particularly the ductus arteriosus which can 'steal' up to 70% of the left ventricular output.(29) Conventional echocardiographic measures to identify PH, particularly TR, may not be very reliable. A recent systematic review of echocardiographic measures used to diagnose PH in CLD reported an inconsistent correlation between TR and PH.(30)

TDI is an alternative technique of assessing myocardial function, and in the last decade various groups of investigators (including our group) have established the feasibility of performing TDI measurements in preterm and term infants.(12-14) Its utility has been studied in different preterm populations e.g. infants with haemodynamically-significant PDA, following surgical ligation of PDA and infants receiving blood transfusions.(22-24). TDI

processes the Doppler signals from the myocardium and allows measurement of myocardial velocities during both contraction and relaxation phases.(31) Myocardial performance index (MPI) is a simple ratio derived from various time intervals of the cardiac cycle (figure 1) and provides a quantitative assessment of combined systolic and diastolic function of the myocardium(32); a higher MPI indicating myocardial dysfunction. Although MPI was originally derived from standard pulse wave Doppler velocities, it can also be derived using TDI waveforms and the reliability of this method has been established.(21)

In our study, myocardial function, as assessed by the conventional methods of LVFS and LVO, was not different between infants in the 3 groups. Yates *et al* reported similar findings in CLD infants and hypothesised that TDI derived indices may be more sensitive than conventional techniques.(6) In our cohort biventricular MPIs in CLD infants requiring positive pressure airway support (group 1) were higher than those obtained from CLD infants requiring low flow oxygen (group 2) which were higher than those from non-CLD infants (group 3) suggesting relative biventricular dysfunction that correlated with severity of CLD. Yates also found that the myocardial velocities and MPIs were abnormal in CLD infants, although they did not reach statistical significance.(6) Kazanci *et al* also demonstrated higher biventricular MPIs in older infants with CLD compared to controls(8) and Czernik *et al* reported elevated RV MPIs in preterm infants with evolving CLD at 28 days of age.(33) These data and the current study suggest that MPI derived from TDI may be a more useful measure of myocardial dysfunction compared to LVFS and LVO.

Previous studies have demonstrated that some infants with CLD have echocardiographic indicators of PH (10,11) which persist until at least early childhood (34,35) and may normalise by the end of first decade.(18) In this study we evaluated the most commonly

used conventional echocardiographic measures of pulmonary hypertension i.e. TR and septal flattening (9) and compared them to RV-IVRT measured using TDI as an indirect measure of pulmonary hypertension. RV-IVRT has been shown to correlate well with pulmonary arterial systolic pressure in adults - the longer the IVRT higher the pulmonary arterial systolic pressure - and it may be more useful than measuring tricuspid regurgitant jet velocity (TR).(15-17) Yates *et al* determined RV-IVRT in infants with CLD and found an increasing trend with increasing severity of CLD.(6) Kazanci *et al* also found that infants with CLD had prolonged RV-IVRT compared to healthy controls.(8) In our study we have demonstrated that RV-IVRT is significantly prolonged in preterm infants with CLD compared to those without CLD. However, conventional echocardiographic measures did not indicate elevated pulmonary blood pressure. Our data suggest prolonged RV-IVRT may be more sensitive than TR and ventricular septal flattening at detecting high pulmonary pressures in infants with CLD. Further studies are needed to identify a threshold value for RV-IVRT that would identify clinically significant PH.

Sub-group analysis showed that infants with CLD who received postnatal dexamethasone for the management of CLD and those requiring supplemental oxygen at discharge had higher MPIs. Both these results support the hypothesis that infants with more severe CLD have relative myocardial dysfunction. However, larger studies are needed to evaluate the clinical significance of this finding.

We found that the peak systolic myocardial velocity at LTA in group 1 infants with CLD was higher compared to infants without CLD. In the sub-group analyses similar higher systolic velocities were detected at MMA and LTA in infants who required supplemental oxygen at discharge. This is in contradiction to the MPI measurements. However, this finding is in

keeping with the study by Yates *et al* who also noted that the peak systolic velocities were higher in infants with severe CLD compared to infants with no or mild CLD. We can only hypothesize that the increased velocity of contraction might be an attempt by the myocardium to compensate for the increased pulmonary vascular resistance and this also warrants further investigation in larger studies.

Other limitations to our study are, although it is the largest study to date in infants with CLD at 36 weeks CGA, the sample size is relatively small. Although TDI-derived measurements may be more sensitive than conventional techniques in detecting myocardial dysfunction, they are not entirely independent of preload and after-load conditions.(23) The TDI measurements obtained in this study reflect myocardial motion in the longitudinal plane only and do not provide information about myocardial motion in other planes. We did not measure right ventricular output (RVO) in this study as the reproducibility is not well established and is more prone to error - the elasticity of the pulmonary arterial walls during systole, and the fact that the pulmonary valves are parallel to ultrasound beams during echocardiography (c.f. aortic valves which are perpendicular making measurement more reliable).(36)

Using TDI-derived assessments of myocardial function, we have shown that preterm infants with CLD have evidence of relative biventricular dysfunction compared to those without CLD. TDI also identified prolongation of RV-IVRT in preterm infants with CLD inferring higher pulmonary arterial blood pressure in these patients. TDI-derived indices may be more sensitive at detecting myocardial dysfunction in CLD compared to LVFS and LVO.

MPI and RV-IVRT derived from TDI measurements may offer neonatologists a novel way of monitoring infants with CLD.

CONFLICTS OF INTEREST: None

What is already known on this subject:

1. Tissue Doppler imaging is feasible in preterm infants
2. Neonatal chronic lung disease (CLD) is associated with long term cardiovascular complications.
3. Pulmonary hypertension complicating CLD is associated with high mortality

What this study adds:

1. CLD is associated with relative biventricular dysfunction at 36w CGA.
2. TDI derived indices may demonstrate evidence of myocardial dysfunction in CLD not identified by conventional echocardiographic measurements.
3. TDI derived RV-IVRT is a potentially useful indirect measure of pulmonary arterial blood pressure in preterm infants with CLD.

FIGURE 1 LEGEND:

This figure shows the waveform obtained using TDI from Lateral tricuspid annulus. **S'** = peak systolic velocity representing systolic function. **E'** and **A'** = early and late diastolic velocities representing diastolic function. **MPI** = myocardial performance index is calculated from **(a-b/b). a** is time interval between the end and beginning of diastolic velocities; **b** is ejection time. **IVCT =** isovolumetric contraction time and **IVRT** = isovolumetric relaxation time.

References:

1. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357(19):1946-55.

2. Bolton CE, Stocks J, Hennessy E, et al. The EPICure study: association between haemodynamics and lung function at 11 years after extremely preterm birth. J Pediatr. 2012;161(4):595-601.

3. Doyle LW, Faber B, Callanan C, et al. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006;118:108-13.

4. Baker CD, Abman SH, Mourani PM. Pulmonary Hypertension in Preterm Infants with Bronchopulmonary Dysplasia. Pediatr Allergy Immunol Pulmonol. 2014;27(1):8-16.

5. Dhillon R. The management of neonatal pulmonary hypertension. Arch Dis Child Fetal Neonatal Ed. 2012;97(3):F223-8.

6. Yates AR, Welty SE, Gest AL, Cua CL. Myocardial tissue Doppler changes in patients with bronchopulmonary dysplasia. J Pediatr. 2008;152(6):766-70.

7. Mourani PM, Ivy DD, Rosenberg AA, et al. Left ventricular diastolic dysfunction in bronchopulmonary dysplasia. J Pediatr. 2008;152(2):291-3.

8. Kazanci E, Karagoz T, Tekinalp G, et al. Myocardial performance index by tissue doppler in bronchopulmonary dysplasia survivors. Turk J Pediatr 2011;53:388–96.

9. Wardle AJ, Wardle R, Luyt K, Tulloh R. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. Arch Dis Child. 2013;98(8):613-7.

10. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics. 2007;120(6):1260-9.
11. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics. 2012;129(3):e682-9.
12. Negrine RJ, Chikermane A, Wright JG, Ewer AK. Assessment of myocardial function in neonates using tissue Doppler imaging. Arch Dis Child Fetal Neonatal Ed. 2012;97(4):F304-6.
13. Mori K et al. Pulsed wave Doppler tissue echocardiography assessment of the long axis function of the right and left ventricles during the early neonatal period. *Heart* 2004;90:175 – 180.
14. Lee A, Nestaas E, Liestøl K, Brunvand L, Lindemann R, Fugelseth D. Tissue Doppler imaging in very preterm infants during the first 24 h of life: an observational study. Arch Dis Child Fetal Neonatal Ed. 2014;99(1):F64-9.
15. Zimbarra Cabrita I, Ruísanchez C, Grapsa J, et al. Validation of the isovolumetric relaxation time for the estimation of pulmonary systolic arterial blood pressure in chronic pulmonary hypertension. Eur Heart J Cardiovasc Imaging. 2013;14(1):51-5
16. Caso P, Galderisi M, Cicala S, et al. Association between myocardial right ventricular relaxation time and pulmonary arterial pressure in chronic obstructive lung disease: analysis by pulsed Doppler tissue imaging. J Am Soc Echocardiogr. 2001;14(10):970-7.

17. Ionescu AA, Ionescu AA, Payne N, et al. Subclinical right ventricular dysfunction in cystic fibrosis. A study using tissue Doppler echocardiography. Am J Respir Crit Care Med. 2001;163(5):1212-8.
18. Joshi S, Wilson DG, Kotecha S, et al. Cardiovascular function in children who had chronic lung disease of prematurity. Arch Dis Child Fetal Neonatal Ed. 2014;99(5):F373-9.
19. Madar J. M-Mode Echocardiography. In: Skinner J, Alverson D, Hunter S (Editors). Echocardiography for the Neonatologist. Churchill Livingstone. 2000:51-58
20. Alverson DC, Eldridge MW, Johnson JD, et al. Noninvasive measurement of cardiac output in healthy preterm and term newborn infants. Am J Perinatol 1984;1:148-51.
21. Harada K, Tamura M, Toyono M, Yasuoka K. Comparison of the right ventricular Tei index by tissue Doppler imaging to that obtained by pulsed Doppler in children without heart disease. Am J Cardiol. 2002;90(5):566-9.
22. Parikh R, Negrine RJ, Chikermane A, Rasiah SV, Ewer AK. Assessment of myocardial function in preterm infants with patent ductus arteriosus using tissue Doppler imaging. Cardiol Young. 2015;25(1):70-5
23. El-Khuffash AF, Jain A, Dragulescu A, et al. Acute changes in myocardial systolic function in preterm infants undergoing patent ductus arteriosus ligation: a tissue Doppler and myocardial deformation study. J Am Soc Echocardiogr. 2012;25(10):1058-67.
24. Saleemi MS, Bruton K, El-Khuffash A, et al. Myocardial assessment using tissue doppler imaging in preterm very low-birth weight infants before and after red blood cell transfusion. J Perinatol. 2013;33(9):681-6.

25. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed 2007;92:F424-7.
26. Doyle LW, Davis PG, Morley CG, et al. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics. 2006;117: 75-83.
27. Rein AJ, Sanders SP, Colan SD, et al. Left ventricular mechanics in the normal newborn. Circulation. 1987;76(5):1029-36.
28. James AT, Corcoran JD, Jain A, et al. Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period. Early Hum Dev. 2014;90(12):829-35.
29. Broadhouse KM, Price AN, Durighel G, et al. Assessment of PDA shunt and systemic blood flow in newborns using cardiac MRI. NMR Biomed. 2013;26(9):1135-41.
30. Nagiub M, Lee S, Guglani L. Echocardiographic Assessment of Pulmonary Hypertension in Infants with Bronchopulmonary Dysplasia: Systematic Review of Literature and a Proposed Algorithm for Assessment. Echocardiography. Published online First: 18 September 2014. doi: 10.1111/echo.12738.
31. Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. Circulation. 2006;113(10):e396-8.
32. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy. J Cardiol. 1995 Dec;26(6):357-66.

33. Czernik C, Rhode S, Metze B, et al. Persistently elevated right ventricular index of myocardial performance in preterm infants with incipient bronchopulmonary dysplasia. PLoS One. 2012;7(6):e38352.
34. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med 2004;170:1006–13.
35. Subhedar NV, Shaw NJ. Changes in pulmonary arterial pressure in preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2000;82(3):F243-7.
36. Alverson DC. Cardiac Output. In: Skinner J, Alverson D, Hunter S (Editors). Echocardiography for the Neonatologist. Churchill Livingstone. 2000:121-131.