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Longitudinal echocardiographic parameters for evaluation of pulmonary hypertension in preterm infants with very low birth weight

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Abstract

Background: Echocardiography is essential for the evaluation of pulmonary hypertension. We determined the feasible quantitative parameter for screening and monitoring pulmonary hypertension in preterm infants. *Methods:* This secondary analysis of a prospective cohort single-centre study was conducted between August 2019 and September 2020. Serial echocardiography was performed 7 and 28 days after birth and at 36 weeks postmenstrual age. The data of infants who developed pulmonary hypertension at 36 weeks postmenstrual age were compared with those without pulmonary hypertension. We also modelled the parameters' trend and performed an interaction test using multi-level Gaussian regression. *Results:* Out of 30 infants enrolled in the study, 79 echocardiograms were analysed. Left ventricular eccentric index was obtainable in all infants, while tricuspid jet velocity was measurable in 44.1%. Left ventricular eccentric index correlated well with tricuspid regurgitation jet velocity ($r = 0.77$, $P < 0.001$). Six infants were diagnosed with newly developed or persistent pulmonary hypertension at 36 weeks postmenstrual age. Serial left ventricular eccentric index showed a significantly different increasing trend in the pulmonary hypertension group (change per day: +0.004; $P = 0.090$) from the decreasing trend among a non-pulmonary hypertension group (change per day: –0.001; $P = 0.041$) (P for interaction = 0.007). Right ventricular systolic function and right ventricular isovolumic systolic velocity revealed a reducing trend in the pulmonary hypertension group, which was different from the improving trend in non-pulmonary hypertension infants. Infants with low current weight, low postmenstrual age, and requiring high-flow oxygen therapy at day 28 of life trended to increase the risk of late pulmonary hypertension. *Conclusion:* Left ventricular eccentric index and right ventricular isovolumic systolic velocity were feasible for assessing pulmonary hypertension and should be incorporated into pulmonary hypertension evaluation. Serial left ventricular eccentric index and right ventricular isovolumic systolic velocity may help predict late pulmonary hypertension and early detection of right ventricular dysfunction.

Introduction

Elevated pulmonary vascular pressures are typically observed in fetal life and partially decrease in response to oxygen after birth. The presence of persistent pulmonary hypertension indicates a failure in this transition.[1] Pulmonary hypertension has been reported in 23–37% of premature infants.[2,3] Those with persistent pulmonary hypertension beyond the first few months of life had a high mortality rate.[4] When pulmonary hypertension was severe, 47% of them died by two years of age.[4,5]

Increased pulmonary vascular resistance results from pulmonary vascular remodelling, leading to right ventricular hypertrophy and failure. Right ventricular dysfunction due to increased afterload is a primary driver of disease severity in pulmonary hypertension patients.[6] Cardiac catheterisation is the gold standard for haemodynamic assessment of pulmonary vascular resistance or pulmonary artery pressure, but it is an invasive procedure.[6] Echocardiography is a non-invasive and more available tool for the evaluation of pulmonary hypertension in very low birth weight infants. Tricuspid regurgitation jet velocity is a widely utilised echocardiographic parameter to evaluate pulmonary hypertension, quantitating pulmonary artery pressure. Tricuspid regurgitation jet velocity correlated well with the invasive haemodynamic measurement when performed with a good window view and small

insonation angle.[7,8] However, a tricuspid regurgitation jet was present in only 14–80% of paediatric echocardiograms for pulmonary hypertension.[9,10] Thus, tricuspid regurgitation jet velocity may not be feasible for treatment effect monitoring or longitudinal analysis of the disease. Qualitative septal flattening is also commonly used in newborn patients.[8,11–13] When the right to left ventricular pressure ratio increases, the septum becomes more flattened with reversed curvature in severe right ventricular hypertension.[10] However, septal flattening is a subjective assessment with significant interobserver variability.[11,14] Left ventricle eccentricity index quantifies septal flattening and is reproducible with less intra- and interobserver variability[15–17] Utilisation of left ventricle eccentricity index, pulmonary artery acceleration time, and right/left ventricle dimension ratio to quantify pulmonary hypertension is established in adults and has been increasingly studied in children.[7,10,14] Still, data are limited in preterm infants.[14,16]

Assessment of the right ventricular function is the key to determine disease severity and prognosis.[18] Tricuspid annular plane systolic excursion and fractional area change are parameters to assess right ventricular function in preterm infants.[19,20] Tissue Doppler imaging is a technique currently used to evaluate ventricular function by measurement of myocardial motion velocities during systole and diastole in infants with bronchopulmonary dysplasia.[21,22] However, its application for pulmonary hypertension screening and monitoring has not been well characterised and is still challenging in the very premature heart.[23] This study aimed to determine the feasibility of quantitative echocardiography parameters for pulmonary hypertension screening and analyse longitudinal changes up to 36 weeks postmenstrual age in pulmonary pressure and right ventricular function in very low birth weight infants. Secondary objectives were to determine the predictive factors associated with newly developed or persistent pulmonary hypertension at 36 weeks postmenstrual age. Standardising screening and follow-up will allow for the early detection, objective monitoring, risk stratification, and effective management of infants with pulmonary hypertension.[11]

Materials and methods

Study population

This study was a secondary analysis of a prospective cohort single-centre study. The primary analysis of this prospective cohort single-centre study is the feasibility of pulmonary hypertension screening in very low birth weight infants at risk of bronchopulmonary dysplasia by using tricuspid regurgitation gradient and a cardiac biomarker. It was conducted in the neonatal intensive care unit between August 1, 2019, and September 30, 2020, and was approved by the Institutional Ethics Committee. Preterm infants with a birth weight of 400 g–1,500 g or gestational age $23^{0/7}$–$31^{6/7}$ weeks admitted within 24 hours of age were enrolled. Exclusion criteria included congenital heart diseases [except patent ductus arteriosus, non-significant atrial septal defect, or non-significant ventricular septal defect], chromosomal abnormalities, multiple congenital anomalies, hydrops fetalis, cardiomyopathy, diaphragmatic hernia, or administration of a fluid bolus ≥10 ml/kg intravenously in the past 24 hours to avoid volume load dependence that might interfere with evaluating ventricular function. After obtaining informed consent from parents, the infants received pulmonary hypertension screening according to Chiang Mai University protocol. Preterm infants with gestational age <28 weeks and body weight <1,000 g underwent echocardiographic screenings at 7 and 28 days of age and at 36 weeks postmenstrual age. Preterm infants with gestational age $28^{0/7}$–$31^{6/7}$ and body weight 1,000 g–1,500 g underwent echocardiographic screening at 28 days of age and at 36 weeks postmenstrual age (Supplemental Figure 1).

Definitions

- Criteria for pulmonary hypertension: left ventricular eccentricity index ≥1.2[7, 24]
- Very low birth weight: birth weight of less than 1500 g
- Extremely low birth weight: birth weight of less than 1000 g
- Small for gestational age: birth weight of less than 10th percentile for gestational age
- Birth asphyxia: Activity, Pulse, Grimace, Appearance, Respiration (APGAR) score of <7 at 5 minutes
- Haemodynamically significant patent ductus arteriosus: patent ductus arteriosus size ≥1.5 mm and left atrial-to-aortic root ratio ≥1.5
- High-flow nasal cannula: the gas flow is operated between 3–8 L/min

Clinical data

Demographic data, including sex, gestational age, birth weight, history of asphyxia, route of delivery, extensive resuscitation at birth, intrauterine growth restriction, small for gestational age, and respiratory support, were collected.

Echocardiographic data

All echocardiograms were performed using a Philips CX 50 and Phillips Epiq 7 with 8,12 MHz probes (Philips Medical Systems) according to patient size. The data were collected and analysed by a single observer (YP). Non-significant intracardiac shunts such as atrial septal defect, patent foramen ovale, and ventricular septal defect were examined. Patent ductus arteriosus was identified by 2D, colour Doppler, and shunt gradient. Left atrial-to-aortic root ratio was measured to determine left heart volume loading.[25]

Echocardiographic determination of pulmonary hypertension and pulmonary vascular resistance

Pulmonary artery pressure was estimated using tricuspid regurgitation jet velocity if tricuspid regurgitation jet was present. Tricuspid regurgitation jet velocity was measured using continuous-wave Doppler from an apical four-chamber view.[26] Left ventricle eccentricity index was measured as the diameter in the parasternal short-axis view at the midpapillary muscle level during end-systole.[17] Left ventricular eccentricity index was calculated as follows: left ventricle eccentricity index = left ventricular diameter parallel to the interventricular septum/left ventricular diameter perpendicular to the interventricular septum.[7,17] The pulmonary artery velocity wave Doppler was used to calculate the pulmonary artery acceleration time and right ventricular ejection time.[19]

Echocardiographic determination of right ventricular function

Tricuspid annular plane systolic excursion was measured by M-mode recording in the apical four-chamber view with the cursor placed at the free wall of the tricuspid valve annulus.[20] Fractional area change was measured by manual tracing of the right ventricular endocardial border from the lateral tricuspid annulus along the free wall to the apex and back along the interventricular

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septum to the medial tricuspid valve annulus at end-diastole and end-systole.[27] For tissue Doppler imaging, the right ventricular myocardial velocities were measured with pulse-wave tissue Doppler imaging at the lateral tricuspid annulus from an apical four-chamber view.[28] The insonation angle should be less than 15°. The mean of 3−5 consecutive cardiac cycles was obtained for each echocardiographic parameter. Peak isovolumic systolic velocity and peak systolic ejection velocity (S) were used to quantify systolic velocities, which corresponded to early systolic isovolumic contraction and later systolic contraction ejection phases, respectively.[29] Diastolic velocities measured were the early diastolic E' velocity corresponding to early diastolic relaxation and later diastolic A' velocity, corresponding to atrial contraction.[30] Right ventricular myocardial performance index was obtained by the sum of isovolumic contraction and relaxation time divided by ejection time derived from tissue Doppler imaging.[28]

Echocardiographic determination left ventricular function

Mitral annular plane systolic excursion was measured by M-mode recording in the apical four-chamber view with the cursor placed at the free wall of the mitral valve annulus. Left ventricular ejection fraction was measured by M-mode in the left ventricular short-axis view.[31]

Statistical analysis

All statistical analyses were performed using Stata 17 (StataCorp, College Station, Texas, USA). We described categorical variables with frequency and percentage. For continuous variables, mean and standard deviation or median and interquartile range were used for data description depending on the underlying distribution.

An independent *t*-test or Mann–Whitney *U* test was used to compare the difference of continuous variables between groups, whereas Fisher's exact probability test was used for categorical variables. We also calculated the standardised difference and an area under the receiver operating characteristics curve for each predictor. Multivariable analysis was not performed as a means to identify significant predictors of pulmonary hypertension at postmenstrual age 36 weeks, owing to significant limitations in terms of study size. *P*-value < 0.05 was defined as significant statistical testing. In this study, we defined significant predictors of pulmonary hypertension based on three criteria: (1) statistical testing at *P*-value ≤ 0.1, (2) a lower bound of 95% confidence interval of an area under the receiver operating characteristic curve ≥ 0.5, and (3) a standardised difference ≥ 0.5 (moderate effect size according to Cohen).[32]

Individual profile plots were illustrated to visualise the changes in echocardiographic parameters over time. We modelled the trend of these values and performed an interaction test using multi-level Gaussian regression. Pearson's correlation coefficient and correlation plots were used to quantify the strength of a linear relation between left ventricular eccentricity index and tricuspid regurgitation jet velocity.

Results

Thirty-three infants were enrolled in the study, but three were excluded due to missing echocardiograms. The final enrolled number was 30, with no patient death up to 36 weeks postmenstrual age. Fourteen infants (46.67%) were male. A total of 79 echocardiograms were analysed. No patients received a pharmacological pulmonary vasodilator during the echocardiographic study. Nineteen infants (63.33%) had extremely low birth weight (gestational age 27.07 ± 2.51 weeks and weight 1181.43 ± 507.89 g). Eleven infants (36.67%) had very low birth weight (gestational age 29.63 ± 0.94 weeks and mean weight 1861.59 ± 462.95 g). Of the entire cohort, 18 (22.8%) events were diagnosed as pulmonary hypertension. The prevalence of pulmonary hypertension was 31.6% (6/19) on day 7 of life and 20% (6/30) on day 28 of life. The final six infants (6/30, 20%) had persistent or progressive pulmonary hypertension at 36 weeks postmenstrual age. Three patients presented with pulmonary hypertension at the last echocardiography. Three patients who presented with at least one prior echocardiography showed evidence of pulmonary hypertension before the last echocardiography.

No significant differences in clinical data were observed at baseline, day 7 of life, and 36 weeks postmenstrual age, with the exception that male infants were more likely to be in the pulmonary hypertension group than the non-pulmonary hypertension group (Tables 1, 2, and 3).

At day 28, infants with late pulmonary hypertension had significantly lower current weight and postmenstrual age than the non-pulmonary hypertension group (975 ± 204.45 g. vs. 1300.95 ± 402.68 g., $P = 0.067$, receiver operating characteristic curve = 0.73) and (30.48 ± 1.32 wk vs. 32.64 ± 2.51 wk, $P = 0.052$, receiver operating characteristic curve = 0.78), respectively (Table 3). Infants with late pulmonary hypertension also required high-flow oxygen therapy at day 28 more than those without pulmonary hypertension. No differences were noted in patent ductus arteriosus to body weight ratio, size, and left atrium to aorta ratio between the pulmonary hypertension group and the non-pulmonary hypertension group.

Echocardiography data

Tricuspid regurgitation was presented and interpretable in 35 of 79 (44.30%) echocardiograms. Tricuspid regurgitation jet velocity correlated with left ventricular eccentricity index ($r = 0.77$, $P = 0.005$) (Figure 1). Left ventricular eccentricity index was performed successfully in all examinations. All infants with tricuspid regurgitation jet velocity >25 mmHg (2.5 m/sec) also had left ventricular eccentricity index >1.2. Tissue Doppler imaging at the lateral tricuspid annulus (right ventricular peak isovolumic systolic velocity, S', *E*,' A' and myocardial performance index) was available for interpretation in 72 of 79 (91%) echocardiograms.

The longitudinal changes in echocardiography parameters (Fig. 2)

Left ventricular eccentricity index showed a significantly different trend, increasing over time in the pulmonary hypertension group and decreasing over time in the non-pulmonary hypertension group ($P = 0.007$). The mean change per day in the pulmonary hypertension group was +0.004 ($P = 0.090$). The mean change in the non-pulmonary hypertension group was −0.001 ($P = 0.041$). Right ventricular peak isovolumic systolic velocity trend showed a progressive worsening of right ventricular function in the pulmonary hypertension group, which was the opposite of the improving function found in the non-pulmonary hypertension group ($P = 0.197$).

Echocardiography parameters at 7 days of age (Table 2)

Compared to the non-pulmonary hypertension group, there was no significant difference between the two groups regarding the size of patent ductus arteriosus and patent ductus arteriosus by body

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Table 1. Baseline fixed factors

Factors	Overall $N = 30$		PHT at 36 days $N = 6$		No PHT at 36 weeks PMA $N = 24$		Standardised difference	*P*-value	ROC (95% CI)
Birth weight (g) mean ± SD	898.57	257.89	760	198.32	933.20	262.76	0.744*	0.144	0.67 (0.45 – 0.89)
Sex (male), *n* (%)	14	46.67	5	83.33	9	37.50	−1.011*	0.072**	0.73 (0.54 – 0.92)***
Gestational age (wk) (mean ± SD)	28.01	2.44	26.85	2.29	28.29	2.43	0.612*	0.199	0.67 (0.40 – 0.94)
IUGR/SGA, *n* (%)	9	30	1	16.67	8	33.33	0.373	0.637	0.58 (0.39 – 0.77)
Bronchopulmonary dysplasia, *n* (%)	12	40	5	83	7	29	−1.239	0.026**	0.77(0.58-0.96)***
Rout of delivery, *n* (%)									
Normal delivery	12	40	2	33.33	10	41.67	−0.163	1.000	0.54 (0.31 – 0.77)
Caesarean section	18	60	4	66.67	14	58.33			
Resuscitation at birth, *n* (%)									
nCPAP	8	26.67	2	33.33	6	25.0	0.169	1.000	0.54 (0.31 – 0.77)
PPV	1	3.33	0	0	1	4.17			
ETT	20	66.67	4	66.67	16	66.67			
Chest compression	1	3.33	0	0	1	4.17			
Inotropic drug	0	0	0	0	0	0			
Extensive resuscitation (including ETT or chest compression or inotropic drug), *n* (%)	21	70	4	66.67	17	70.83	0.084	1.000	0.52 (0.29 – 0.74)
Asphyxia, *n* (%)	4	13.33	2	33.33	2	8.33	−0.601*	0.169	0.63 (0.41 – 0.84)
Ventricular septal defect, *n* (%)	2	6.67	1	16.67	1	4.17	−0.387	0.366	0.56 (0.39 – 0.73)

APGAR: Activity, Pulse, Grimace, Appearance, Respiration; Asphyxia: APGAR at 5 min score <7; ETT = endotracheal tube; IUGR = intrauterine growth restriction; nCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age;
PPV = positive pressure ventilation; ROC = receiver operating characteristic curve; SGA = small for gestational age; *standardised difference ≥ 0.5; **statistical testing at *P*-value ≤ 0.1; ***lower bound of 95% confidence interval of an area under ROC curve ≥ 0.5.

weight ratio. Although the number of infants having tricuspid regurgitation jet velocity was significantly higher in the non-pulmonary hypertension group, tricuspid regurgitation jet velocity was in the normal range (4.5 mmHg [IQR 0,10.5]). Two infants in the late pulmonary hypertension group had early pulmonary hypertension at day 7 of life. The ratio of early pulmonary hypertension was higher in late pulmonary hypertension (33.3%) than in non-pulmonary hypertension infants (12.7%) but was not statistically significant.

Echocardiography parameters at 28 days of age (Supplemental Table1)

Two infants in the late pulmonary hypertension group met pulmonary hypertension criteria at day 28 of life. There was no difference in echocardiographic parameters between the late pulmonary hypertension group and the non-pulmonary hypertension group.

Echocardiography parameters at 36 weeks postmenstrual age (Table 3)

Tricuspid regurgitation jet velocity was significantly higher in the pulmonary hypertension group than the non-pulmonary hypertension group (28.5 mmHg [IQR 21.5, 48.5] vs. 13 mmHg [IQR 0, 21], $P = 0.012$). Right ventricular peak isovolumic systolic velocity was significantly reduced in the pulmonary hypertension group (5.5 ± 2.16 cm/sec vs. 7.69 ± 1.93 cm/sec, $P = 0.025$), and right ventricular myocardial performance index in the pulmonary hypertension group was significantly prolonged compared to the non-pulmonary hypertension group (0.43 ± 0.11 vs. 0.35 ± 0.05, $P = 0.033$).

Discussion

Twenty percent (6/30) of preterm low birth weight infants were diagnosed with newly developed or persistent pulmonary hypertension at 36 weeks postmenstrual age in our study. This prevalence is slightly higher than 11.7–14% in previous prospective screening of pulmonary hypertension,[12,13] probably due to different diagnostic criteria of pulmonary hypertension and no pulmonary vasodilator treatment in our study. In our study, small for gestational age was not significantly different between the two groups of patients. A previous review article showed that poor growth in utero may be one of the risk factors for bronchopulmonary dysplasia and may cause pulmonary hypertension.[33] A recent study showed premature infants suffering from bronchopulmonary dysplasia have a tendency to experience pulmonary hypertension.[34] We had a similar finding in that the late pulmonary hypertension group had a higher incidence of bronchopulmonary dysplasia than the other group. In our study, preterm infants who still needed high-flow oxygen therapy at 28 weeks of age were likely to develop pulmonary hypertension at 36 weeks postmenstrual age, consistent with the study of Bhat et al.[12] Prolonged oxygen therapy in infants with abnormal lung development may contribute to bronchopulmonary dysplasia and pulmonary hypertension.[1] The haemodynamic significance of patent ductus arteriosus or patent

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Table 2. Dynamic factors at 7 days in preterm infants with BW <1,000 g ($N = 19$)

Factors	PHT at 36 weeks PMA $N = 5$		No PHT at 36 weeks PMA $N = 14$		Standardised difference	*P*-value	ROC (95% CI)
Current weight (g), mean ± SD	741.6	193.83	729.71	179.49	−0.063	0.902	0.51 (0.18–0.85)
Post menstrual age (wk), mean ± SD	27.32	1.38	28.96	2.82	0.739*	0.233	0.66 (0.41–0.90)
Systolic blood pressure (mmHg), mean ± SD	69.2	13.73	70.29	10.49	0.088	0.856	0.45 (0.10–0.82)
Diastolic blood pressure (mmHg), mean ± SD	41	9.21	39.14	7.96	−0.215	0.664	0.56 (0.26–0.87)
All PDA treatment, *n* (%)							
No treatment	2	40.0	9	64.29	−0.332	0.872	0.61 (0.32–0.89)
Fluid restriction	1	20.0	2	14.29			
Diuretics	1	20.0	1	7.14			
Surgical ligation	1	20.0	2	14.29			
Echocardiography parameters							
Atrial septal defect, *n* (%)	5	100	12	85.71	−0.556*	1.000	0.57 (0.48–0.67)
Patent ductus arteriosus, *n* (%)	2	40.0	3	21.43	−0.378	0.570	0.59 (0.33–0.86)
Patent ductus arteriosus by body weight (mm/kg), mean ± SD	1.63	0.07	2.09	0.93	0.688*	0.562	0.50 (0–1.00)
LA:Ao (only PDA patients), mean ± SD	1.28	0.11	1.56	0.39	1.009*	0.248	0.83 (0.37–1.00)
Haemodynamic significant PDA, *n* (%)	1	20.0	2	14.29	−0.140	1.000	0.53 (0.31–0.75)
Pulmonary hypertension measurement							
Tricuspid regurgitation, *n* (%)	0	0	8	57.14	1.573*	0.045**	0.79 (0.65–0.92)***
Tricuspid regurgitation velocity (mmHg) in only TR patient, median (IQR)	–	–	4.5	0, 10.5	–	–	–
Tricuspid regurgitation velocity (only TR) / systolic pressure, median (IQR)	–	–	0.06	0, 0.16	–	–	–
LVEI, mean ± SD	1.18	0.12	1.14	0.09	−0.400	0.420	0.56 (0.19–0.92)
LVEI ≥1.2, *n* (%)	2	33.33	3	12.50	−0.477	0.254	0.60 (0.39–0.82)
PA AT (ms), mean ± SD	60.2	13.18	56.92	13.03	−0.250	0.640	0.58 (0.26–0.90)
RV ET (ms), mean ± SD	169.8	15.67	176	25.02	0.296	0.616	0.52 (0.23–0.82)
PA AT/RV ET, median (IQR)	0.3	0.3,0.34	0.32	0.26,0.40	0.331	0.766	0.55 (0.27–0.82)
Right ventricular function							
RV S' (cm/s), mean ± SD	7.46	1.46	6.64	2.87	−0.356	0.559	0.62 (0.34–0.89)
RV E' (cm/s), mean ± SD	7.98	1.63	8.54	3.26	0.216	0.723	0.53 (0.22–0.83)
RV A' (cm/s), mean ± SD	9.86	2.69	10.96	1.46	0.507*	0.316	0.70 (0.32–1.00)
RV IVV (cm/s), mean ± SD	7.6	3.05	7.0	2.13	−0.228	0.646	0.53 (0.22–0.83)
RV MPI, mean ± SD	0.40	0.13	0.39	0.09	−0.042	0.932	0.53 (0.13–0.92)
TAPSE (cm), median (IQR)	0.62	0.56,0.70	0.68	0.62,0.76	0.213	0.634	0.58 (0.25–0.91)
RV FAC (%), mean ± SD	57.18	11.63	55.27	10.97	−0.168	0.749	0.56 (0.25–0.87)
Left ventricular function (mean ± SD)							
MAPSE (cm), median (IQR)	0.41	0.14	0.44	0.13	0.222	0.683	0.55 (0.22–0.88)
LV CO (L/min), median (IQR)	0.26	0.22,0.40	0.29	0.25,0.40	0.176	0.744	0.57 (0.22–0.93)
LV EF (%), mean ± SD	65.82	10.81	66.03	5.79	0.024	0.957	0.63 (0.26–0.99)

A' = late diastolic velocity; E' = early diastolic velocity; S' = peak systolic ejection velocity; AT = acceleration time; CO = cardiac output; EF = ejection fraction; FAC = fractional area change; IVV = peak isovolumetric systolic velocity; LA:Ao = left atrial-to-aortic root ratio; LV = left ventricular; LVEI = left ventricular eccentric index; MAPSE = mitral annular plane systolic excursion; MPI = myocardial performance index; PA = pulmonary artery; PDA = patent ductus arteriosus; PMA = postmenstrual age; ROC = receiver operating characteristic curve; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.
Haemodynamic significant PDA: PDA ≥1.5 mm and left atrial-to-aortic root ratio ≥1.5.
*standardised difference ≥0.5; ** statistical testing at *P*-value ≤ 0.1; *** lower bound of 95% confidence interval of an area under ROC curve ≥0.5.

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Table 3. Dynamic factors at 36 weeks PMA in all preterm infants with BW <1,500 g ($N = 30$)

Factors	PHT at 36 weeks PMA $N = 6$		No PHT at 36 weeks PMA $N = 24$		Standardised difference	*P*-value	ROC (95% CI)
Current weight (g), mean ± SD	1768	308.20	1945.42	398.02	0.497	0.320	0.66 (0.43 – 0.90)
Post menstrual age (wk), mean ± SD	36.46	0.64	36.98	1.28	0.508	0.352	0.60 (0.37 – 0.83)
Systolic blood pressure (mmHg), mean ± SD	74	10.94	72.5	10.78	−0.138	0.763	0.53 (0.24 – 0.82)
Diastolic blood pressure (mmHg), mean ± SD	39.67	8.87	41.13	9.00	0.163	0.725	0.52 (0.25 – 0.79)
Respiratory support, *n* (%)							
Room air	3	50.0	16	66.67	0.323	0.641	0.58 (0.34 – 0.82)
Cannula <1 L/min (low flow)	1	16.67	1	4.17	−0.387	0.366	0.56 (0.39 – 0.73)
Cannula 1–3 L/min (high flow)	1	16.67	4	16.67	0	1.000	0.50 (0.32 – 0.68)
NIPPV, canular >3 L/min	0	0	2	8.33	0.417	1.000	0.54 (0.49 – 0.60)
IPPV	1	16.67	1	4.17	−0.387	0.366	0.56 (0.40 – 0.73)
Cannula ≥ 1 L/min, *n* (%)	2	33.33	7	29.17	−0.085	1.000	0.52 (0.29 – 0.75)
High respiratory support (including NIPPV or cannula >3 L/min or IPPV), *n* (%)	2	33.33	12	50.0	0.324	0.657	0.58 (0.35 – 0.81)
FiO_2, median (IQR)	0.3	0.27,0.4	0.33	0.25, 0.4	−0.092	1.000	0.50 (0.12 – 0.88)
Group of effective FiO_2, *n* (%)							
0.21	3	50.0	17	70.83	0.410	0.372	0.60 (0.36 – 0.84)
0.22 – 0.29	1	16.67	1	4.17	−0.387	0.366	0.56 (0.39 – 0.73)
0.30 – 0.69	2	33.33	6	25.0	−0.173	0.645	0.54 (0.32 – 0.77)
>0.7	0	0	0	0	.	.	.
Echocardiography parameters							
Atrial septal defect or patent foramen ovale, *n* (%)	6	100	23	95.83	−0.288	1.000	0.52 (0.48 – 0.56)
Patent ductus arteriosus, *n* (%)	1	16.67	7	29.17	0.286	1.000	0.56 (0.37 – 0.75)
Patent ductus arteriosus size (mmHg), mean ± SD	0.22	0.53	0.32	0.60	0.188	0.696	0.55 (0.35 – 0.76)
Patent ductus arteriosus by body weight (mm/kg), median (IQR)	0.72	0.72,0.72	0.46	0.29,0.80	.	0.513	0.71 (. – 1.00)
LA:Ao (only PDA patient), median (IQR)	1.56	1.56	1.36	1.26,1.44	.	0.126	1.00 (. – 1.00)
Pulmonary hypertension measurement							
Tricuspid regurgitation velocity (mmHg) in only TR patient median (IQR)	28.5	21.5,48.5	13	0,21	−1.436*	0.012**	0.93 (0.78 – 1.00)***
Tricuspid regurgitation velocity (only TR)/systolic pressure median (IQR)	0.40	0.31,0.62	0.16	0,0.26	−1.674*	0.012**	0.93 (0.78 – 1.00)***
LVEI, mean ± SD	1.40	0.24	1.04	0.91	−2.010*	<0.001**	1.00 (1.00)***
PA AT (ms), mean ± SD	51.28	9.93	59.59	20.56	0.514*	0.351	0.59 (0.36 – 0.83)
RV ET (ms), mean ± SD	183	20.56	188.32	24.85	0.233	0.635	0.56 (0.30 – 0.83)
PA AT/RV ET, median (IQR)	0.3	0.25,0.32	0.29	0.26,0.32	0.462	0.694	0.55 (0.27-0.83)
Right ventricular function							
RV S' (cm/s), mean ± SD	6.72	0.74	7.53	1.58	0.659*	0.237	0.66 (0.45 – 0.87)
RV E' (cm/s), mean ± SD	8.13	2.61	10.40	5.47	0.531*	0.338	0.53 (0.31 – 0.75)
RV A' (cm/s), mean ± SD	9.41	2.51	10.61	3.79	0.373	0.483	0.60 (0.29 – 0.92)
RV IVV (cm/s), mean ± SD	5.5	2.16	7.69	1.93	1.064*	0.025**	0.79 (0.54 – 1.00)***
RV MPI, mean ± SD	0.43	0.11	0.35	0.05	−0.839*	0.033**	0.73 (0.57 – 0.98)***
TAPSE (cm), median (IQR)	0.69	0.63,0.97	0.78	0.70,0.98	0.553*	0.313	0.58 (0.29 – 0.87)
RV FAC (%), mean ± SD	50.58	5.76	51.38	9.02	0.106	0.839	0.57 (0.31 – 0.82)

(*Continued*)

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Table 3. (*Continued*)

Factors	PHT at 36 weeks PMA $N = 6$		No PHT at 36 weeks PMA $N = 24$		Standardised difference	*P*-value	ROC (95% CI)
Left ventricular function							
MAPSE (cm), mean ± SD	0.45	0.14	0.52	0.12	0.515*	0.246	0.68 (0.39 – 0.97)
LVCO (L/min), median (IQR)	0.41	0.35,0.60	0.34	0.25,0.50	−0.588*	0.298	0.64 (0.34 – 0.94)
LVEF (%), mean ± SD	63.37	5.78	65.53	8.49	0.297	0.563	0.59 (0.36 – 0.82)

A' = late diastolic velocity; E' = early diastolic velocity; S' = peak systolic ejection velocity; AT = acceleration time; CO = cardiac output; EF = ejection fraction; FAC = fractional area change; IVV = peak isovolumetric systolic velocity; LA:Ao = left atrial-to-aortic root ratio; LV = left ventricular; LVEI = left ventricular eccentric index; MAPSE = mitral annular plane systolic excursion; MPI = myocardial performance index; PA = pulmonary artery; PMA = postmenstrual age; ROC = receiver operating characteristic curve; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.
*Standardised difference ≥0.5; **statistical testing at *P*-value ≤ 0.1; ***lower bound of 95% confidence interval of an area under ROC curve ≥0.5.

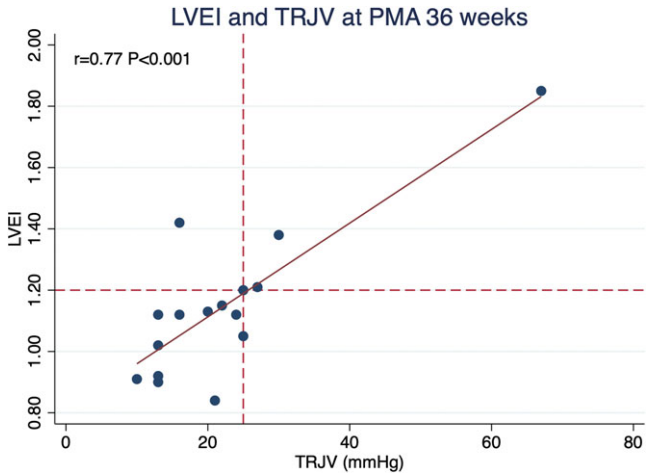

Figure 1. Relation between tricuspid valve jet velocity (TRJV) and left ventricular eccentric index (LVEI) postmenstrual age at 36 weeks; PMA: postmenstrual age.

ductus arteriosus treatment was not related to the late pulmonary hypertension, similar to the findings of Bhat et al.[12] and Mourani et al.[13] In our study, there were no significant differences between the two groups of patients in using invasive positive pressure ventilation, non-invasive positive pressure ventilation, or fractional concentration of administered oxygen, which can be indicators of the disease severity. This could be due to the small sample size.

Echocardiographic evaluation of pulmonary hypertension and right ventricular function

To our knowledge, this is the first prospective serial study of quantitative echocardiographic screening of pulmonary hypertension in preterm infants from day seven and day 28 of life until 36 weeks postmenstrual age. In this study, tricuspid regurgitation jet velocity was measurable in 44.30%, whereas left ventricular eccentricity index was performed successfully in all cases. Further, the left ventricular eccentricity index showed a good correlation with tricuspid regurgitation jet velocity. Previous studies in preterm infants at 36–38 weeks postmenstrual age also revealed 15–66% of measurable tricuspid regurgitation jet velocity,[12,14,16] and 86–100% of available left ventricular eccentricity index,[14–16] with a good correlation between both parameters[14,16]. The measurement of left ventricular eccentricity index is easily obtained in parasternal short-axis view at mid-left ventricle between the two papillary muscles and does not depend on insonation angle, as does the tricuspid regurgitation jet velocity Doppler.[35] However, care must be taken to keep the 2D plane perpendicular to the left ventricular long axis to avoid oblique rotation leading to artifactual septum flattening.[35] Too near to the cardiac base may cause septal distortion by the aortic root, and too near to the apex may not detect the abnormality.[36]

The cut-off left ventricular eccentricity index values to identify the presence of pulmonary hypertension among previous studies[7,10,14,16,17,35] varied from 1.15 to 1.24, probably due to different patient ages, pulmonary hypertension aetiologies, and using reference catheterised data or other echocardiographic parameters to compare. We chose >1.2 as an abnormal ratio to avoid overdiagnosis of pulmonary hypertension.[7] After birth, pulmonary pressure should be high initially. Over time, there should be a gradual decrease in pulmonary pressure, normalising within two weeks. Therefore, left ventricular eccentricity index should return to normal. In infants facing pulmonary hypertension, the progression of left ventricular eccentricity index recovery may be prolonged. Left ventricular eccentricity index >1.2 could differentiate the trend of progressive pulmonary hypertension in late pulmonary hypertension infants from decreasing pulmonary pressure in non-pulmonary hypertension infants. The persistent or progressive increase of pulmonary pressure may reflect ongoing pulmonary vascular disease[18] and prolonged oxygen therapy in these very low birth weight infants.[1] Interestingly, we observed a significant ongoing resolution of pulmonary pressure after 7 days of life until 36 weeks postmenstrual age with an estimated rate of left ventricular eccentricity index changes of –0.004 per day.

Right ventricular peak isovolumic systolic velocity represents the systolic function of right ventricle and was significantly reduced in the late pulmonary hypertension group in this study. Patel et al. also found reduced right ventricular peak isovolumic systolic velocity in term newborns with pulmonary hypertension than in the control group.[21] In another cohort of bronchopulmonary dysplasia infants,[37] both right ventricular peak isovolumic systolic velocity and right ventricular peak systolic ejection velocity (S') were diminished, but only right ventricular peak isovolumic systolic velocity had an association with a longer duration of respiratory support. In our study, serial right ventricular peak isovolumic systolic velocity was likely to differentiate the progressively diminished right ventricular systolic function in late pulmonary hypertension infants from increasing right ventricular systolic function in non-pulmonary hypertension infants. The progressively depressed right ventricular systolic function may result from persistent or progressive increased right ventricular

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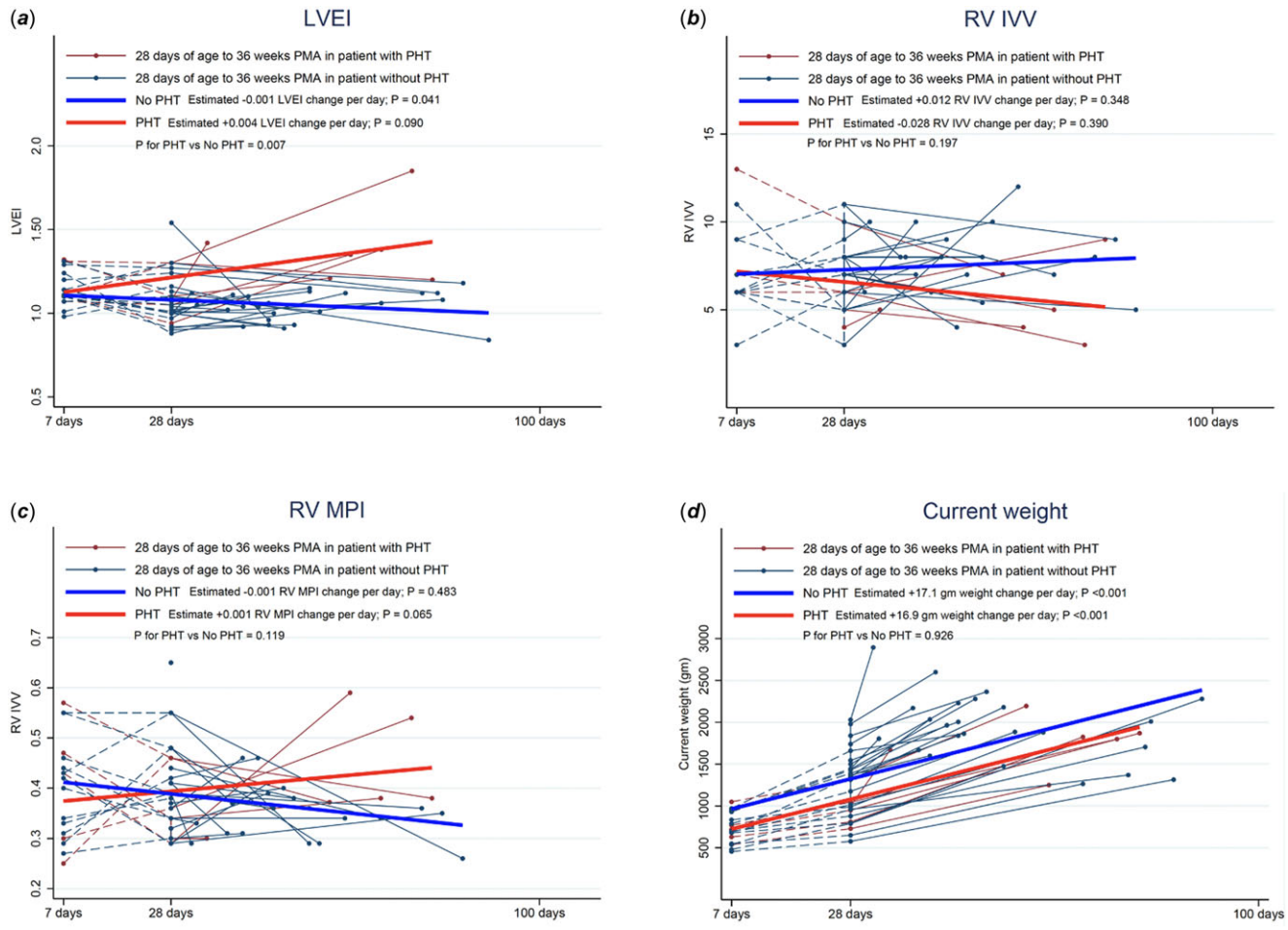

Figure 2. Longitudinal changes of PHT group versus non-PHT group: ***a***) longitudinal change in LVEI, ***b***) longitudinal change in RV IVV, ***c***) longitudinal change in RV MPI, ***d***) longitudinal change in current weight. The thick blue and red lines represent the overall summary trend of the group of patients between PHT and no PHT at 36 weeks PMA. The thin lines represent the individual trends of each patient. LVEI = left ventricular eccentric index; PHT = pulmonary hypertension; RV IVV = right ventricular isovolumic systolic velocity; RV MPI = right ventricular myocardial performance index.

afterload or chronic hypoxia related to impaired pulmonary vascular and alveolar growth and maturation.[18,21,22] The major advantage of right ventricular peak isovolumic systolic velocity measurement is its simplicity and high reproducibility,[29] which should encourage implementation in preterm infants. The limitations of right ventricular peak isovolumic systolic velocity are angle dependency and load dependence, which are similar to other conventional tissue Doppler imaging measurements.[35]

Right ventricular myocardial performance index, which reflects combined systolic and diastolic function, was prolonged significantly in the pulmonary hypertension group at 36 weeks postmenstrual age. This result was consistent with prior studies.[22] However, right ventricular myocardial performance index trends could not differentiate between pulmonary hypertension and non-pulmonary hypertension groups. Pseudo-normalization of myocardial performance index, seen in a patient with increased atrial pressure,[35] may obscure the result.

Right ventricular peak systolic ejection velocity (S'), early diastolic velocity (E'), and tricuspid annular plane systolic excursion seemed to be lower in the pulmonary hypertension group in this study, but there was no statistical significance. Right ventricular fractional area change was not significantly different between the two groups. The above findings emphasise the importance of right ventricular peak isovolumic systolic velocity, which may be an earlier marker of cardiac dysfunction than traditional echocardiographic measurement. Early detection of pulmonary hypertension and right ventricular dysfunction using a suitable quantitative approach could have ramifications for therapeutic options and improve outcomes for pulmonary hypertension patients.

Echocardiographic predictor of late pulmonary hypertension

In this study, late pulmonary hypertension infants had a higher incidence of pulmonary hypertension at day seven or day 28 of life than the non-pulmonary hypertension group, but there were no statistical differences. This result was similar to the study of Mourani et al., which revealed that early pulmonary hypertension at day 7 could predict the late pulmonary hypertension by using septal flattening criteria.[13] The result may have arisen from using different pulmonary hypertension criteria and/or the number of pulmonary hypertension infants in our study was too small to reach statistical significance. A single echocardiographic examination may reveal pulmonary hypertension status

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at that time point. The accurate prediction of late pulmonary hypertension may require serial pulmonary hypertension assessment.

Limitations

The strength of this study is its prospective longitudinal study with well-defined echocardiographic criteria and clinical variables. Furthermore, this study used unbiased screening because the echocardiography was performed by a cardiologist blinded to the patient's diagnosis. However, there were some limitations. First, the initial echocardiogram was performed per protocol, and we did not have data at seven days of age in preterm infants weighing 1000– <1500 g. Longitudinal data in this subgroup may have been lost. Second, there was the lack of simultaneous haemodynamic data obtained by cardiac catheterisation to verify the presence of pulmonary hypertension and optimum left ventricular eccentricity index and right ventricular peak isovolumic systolic velocity cut-off points for clinical use. Third, in some cases, the tricuspid regurgitation gradient could not be measured in the apical 4 chamber view. Parasternal right atrium-right ventricle view is an alternative view for evaluation of tricuspid regurgitation but was not used routinely in this study. Echocardiography protocols should be easy for general paediatricians, and neonatologists to perform, which is why the apical 4 chamber view is the standard view used in this study to access tricuspid regurgitation by visualisation and for measurement. Fourth, this study is a secondary analysis prospective cohort. Some data may not have been presented in this study, including antenatal steroids, history of maternal chorioamnionitis, pre-eclampsia, and preterm prolonged rupture of the membrane, which may be additional predictors of pulmonary hypertension. Future studies should be prospective and include more predictive factors associated with pulmonary hypertension. And lastly, the sample size is small, and clinically relevant findings could have been missed because of limited statistical power. A larger sample size may also identify predictive factors for pulmonary hypertension beyond 36 weeks postmenstrual age.

Conclusion

Left ventricular eccentricity index was feasible for assessing pulmonary hypertension in very low birth weight infants. Serial left ventricular eccentricity index and right ventricular peak isovolumic systolic velocity may help predict late pulmonary hypertension and early detection of right ventricular dysfunction. A study with a larger sample size and more patients with pulmonary hypertension is required to incorporate these parameters into the evaluation and prediction of pulmonary hypertension in preterm infants. We recommend adding both left ventricular eccentricity index and right ventricular peak isovolumic systolic velocity into the echocardiographic assessment of pulmonary hypertension in all very low birth weight infants.

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