

CLINICAL UTILITY OF ECHOCARDIOGRAPHY FOR EARLY AND LATE PULMONARY HYPERTENSION IN PRETERM INFANTS: RELATION WITH BRONCHOPULMONARY DYSPLASIA

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BACKGROUND: We evaluated early and late pulmonary hypertension (PH) in preterm infants and its relation with bronchopulmonary dysplasia (BPD).

METHODS: Sixty-seven preterm infants < 30 weeks' gestation underwent echocardiography within 14 days after birth for early PH and over 28 days after birth for late PH. We measured tricuspid regurgitation (TR) peak velocity, pulse Doppler-derived myocardial performance index (MPI) of right ventricle (RV) (RV MPI), eccentricity index (EI), and tricuspid annular plane systolic excursion (TAPSE).

RESULTS: The median gestation age of patients was 27 weeks (range, 23–30 weeks) and median birth weight was 1030 g (range, 450–1780 g). TR peak velocity was measured only in 19 patients (28.4%). Patients with symptomatic early PH (n = 11) showed a significantly lower systolic EI and a significantly higher incidence of RV MPI > 0.38 and TAPSE < 0.5 cm than patients without PH. The incidence of symptomatic early PH was highest in severe BPD, although this was not statistically significant. Early echocardiographic parameters are not associated with BPD development. Patients with severe BPD showed a significantly higher RV MPI and a significantly higher incidence of RV MPI > 0.38 than patients with mild BPD, and a significantly lower systolic EI and a significantly higher incidence of systolic EI < 0.81 than patients without BPD.

CONCLUSION: Systolic EI, RV MPI, and TAPSE were well represented symptomatic early PH, while systolic EI and RV MPI could be useful parameters for identifying late PH in preterm infants with BPD, even if they did not present PH symptoms.

KEY WORDS: Pulmonary hypertension · Bronchopulmonary dysplasia · Premature birth · Echocardiography.

INTRODUCTION

Pulmonary vascular resistance rapidly falls within the first 24 hours after birth in full-term infants, but the natural course and precise required time of pulmonary transition in preterm infants is not well known. Preterm infants with severe respiratory distress syndrome commonly had persistently elevated pulmonary vascular resistance and right-to-left shunting through the ductus arteriosus.¹⁾ Persistent pulmonary hypertension (PH) in early life of preterm infants may disappear when the underlying cause is corrected, or it may be persistent when complicated with sepsis, pneumonia, and meconium aspiration or an anatomic abnormality.¹⁾ This persistent PH within 2 weeks in preterm infants is called early PH.²⁾

Bronchopulmonary dysplasia (BPD) is the most common complication of preterm birth with the incidence of 68% in infants less than 29 weeks of gestational age.³⁾ Among infants with BPD, those with PH have poor outcomes.³⁾ Gill and Weindling⁴⁾ reported the delayed pulmonary transition and persistent elevated pulmonary pressure after 14 days of life in very low birth weight infant who developed BPD. So, not only PH diagnosed at 36 weeks post-menstrual age (PMA) but also early PH can be associated with BPD.⁴⁾ But the actual incidence and outcome of early PH in preterm infants was not well reported.

Echocardiography is the noninvasive examination of choice for initial screening for PH.⁵⁾ Although the measurement of sys-

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tricuspid pulmonary artery pressure (sPAP) from tricuspid regurgitation (TR) peak velocity is a commonly used and useful parameter for evaluating PH, the lack of a TR jet may lead to an inadequate assessment of pulmonary artery pressures.⁶⁾ Various additional echocardiographic measurements can be used to assess sPAP and right ventricle (RV) dysfunction, such as RV systolic to diastolic time (S/D) ratio, inflection time (InT) and deceleration time (DT) of pulmonary flow, tricuspid annular plane systolic excursion (TAPSE), eccentricity index (EI), and pulse Doppler (PD)-derived myocardial performance index (MPI) or tissue Doppler imaging (TDI)-derived MPI.⁶⁾ However, there is no clear suggestion about which parameter is useful in preterm infants, especially in the neonatal intensive care unit (NICU).

In this study, we performed echocardiographic evaluations using several parameters for early and late PH and we investigated which parameters are useful for identifying PH in preterm infants and how different they are among BPD severities. We also determined whether early PH is associated with BPD development.

METHODS

PATIENTS

We enrolled 67 preterm neonates who were < 30 weeks' gestation, who were admitted to the NICU at Dongsan Medical Center between July 2015 and February 2016. Patients with major congenital heart disease except for patent ductus arteriosus (PDA) and atrial septal defect or with congenital pulmonary anomalies that could influence respiratory function were excluded. We reviewed the patients' medical records and collected data, including prenatal care, birth history, and postnatal clinical course.

Symptomatic early PH was suspected when the patients showed labile oxygenation or differential cyanosis and confirmed by echocardiographic findings such as right-to-left shunting through the ductus or flat interventricular septum (IVS). BPD was diagnosed based on oxygen supplementation at 36 weeks' corrected gestation in an infant who was ≥ 28 days old according to Jobe Bancalari criteria.⁷⁾ BPD severity was classified into mild, moderate, and severe forms according to the fraction of inspired oxygen (FiO₂) or mechanical ventilation as follows: mild BPD without supplemental oxygen, moderate BPD with a FiO₂ < 0.3, and severe BPD with a FiO₂ ≥ 0.3 or positive pressure ventilation.⁷⁾

This study was approved by the Institutional Review Board of the Keimyung University Dongsan Medical Center (approval number: 2016-08-025).

MEASUREMENT OF ECHOCARDIOGRAPHY PARAMETERS

Transthoracic echocardiography was performed within 14 days after birth for early PH and repeated after at least 28 days after birth (over 36 weeks' corrected gestation or before dis-

charge to home) for late PH. All echocardiographic examinations were conducted by a single pediatric cardiologist using a SIEMENS Acuson Sequoia ultrasound scanner with a 10-MHz transducer (Siemens Medical Solutions, Mountain View, CA, USA). We measured TR peak velocity, PD-derived MPI of RV (RV MPI), EI, and TAPSE to assess PH and RV dysfunction. 1) TR peak velocity was obtained by continuous wave Doppler tracing at the tricuspid valve in the apical four-chamber view. 2) RV MPI was estimated using tricuspid valve inflow Doppler images in the apical four-chamber view and RV outflow Doppler images in the parasternal short-axis view. The time from cessation to the beginning of tricuspid inflow (a) and RV ejection time (b) were measured. RV MPI was calculated as follows: RV MPI = (isovolumic contraction time + isovolumic relaxation time)/ejection time = (a - b)/b.⁸⁾ 3) EI was measured as diameter in the parasternal short axis view at the midpapillary muscle level during end-systole and end-diastole. EI was calculated as follows: EI = left ventricular (LV) diameter perpendicular to the IVS / LV diameter parallel to the IVS.⁹⁾ 4) TAPSE was measured by M-mode recordings in the apical four-chamber view with the cursor placed at the free wall of the tricuspid annulus.¹⁰⁾ These parameters could be considered PH when TR peak velocity > 40 mm Hg, RV MPI > 0.38, EI < 0.81, or TAPSE < 0.5 cm.⁶⁾ We also calculated the fractional shortening (FS) of LV as follows: LV FS% = [(LVDd - LVDs)/LVDd] \times 100, where LVDd was the LV dimension at end-diastole and LVDs was the LV dimension at end-systole on standard M-mode echocardiography.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA). Clinical data are described as frequencies and median with range, while echocardiographic measures are described as frequencies and mean \pm standard deviations. The chi-square test was used for categorical data, while the unpaired t test and Mann-Whitney U test were used to compare continuous data between the two groups according to the normality test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

PATIENTS' CLINICAL CHARACTERISTICS

There were, in total, 38 boys and 29 girls with a median gestation age of 27 weeks (range, 23–30 weeks) and median birth weight of 1030 g (range, 450–1780 g). Eleven patients were classified in the symptomatic early PH and 56 were classified in the no PH. Patient demographics and clinical findings are listed in Table 1. The symptomatic early PH group had a significantly lower median gestational age and birth weight than the no PH group ($p = 0.002$ and $p < 0.001$, respectively). There was no significant difference in mode of delivery or prenatal maternal history such as prenatal steroid medication, chorioamni-

Table 1. Patients characteristics

Variables	Early PH (n = 11)	No PH (n = 56)	Total (n = 67)	p value
Sex (male:female)	6:5	32:24	38:29	0.874
Gestational age (weeks)	25 (23–29)	28 (24–30)	27 (23–30)	0.002
Birth weight (g)	750 (450–1110)	1105 (620–1780)	1030 (450–1780)	< 0.001
Gestation (single:multiple)	7:4	31:25	38:29	0.745
Delivery (vaginal:C-section)	2:9	2:54	4:63	0.123
Maternal age (years)	34 (21–41)	33 (25–41)	33 (21–41)	0.997
Prenatal steroid use	10 (90.9)	54 (96.4)	64 (95.5)	0.421
PROM	4 (36.4)	23 (41.1)	27 (40.3)	0.771
Chorioamnionitis	2 (18.2)	16 (28.6)	18 (26.9)	0.714
Oligohydramnios	0 (0)	6 (10.7)	6 (9.0)	0.410
Polyhydramnios	0 (0)	2 (3.6)	2 (3.0)	0.443
Preeclampsia	1 (9.1)	4 (7.1)	5 (7.5)	0.822
Apgar score at 1 minute	4 (1–7)	6 (2–8)	5 (1–8)	0.001
Apgar score at 5 minutes	7 (2–9)	8 (6–9)	8 (2–9)	0.001
NICU admission duration (days)	80 (11–176)	55.5 (7–134)	56 (7–176)	0.248
Duration of ventilator care (days)	13 (1–115)	2 (0–43)	2 (0–115)	< 0.001
Duration of nasal CPAP (days)	46 (0–65)	31 (0–76)	31 (0–76)	0.950
Duration of oxygen use (days)	0 (0–0)	0 (0–38)	0 (0–38)	0.697
Intraventricular hemorrhage	5 (45.5)	9 (16.1)	14 (20.9)	0.043
Retinopathy of prematurity	5 (45.5)	16 (28.6)	21 (31.3)	0.301
Pulmonary hemorrhage	5 (45.5)	2 (3.6)	7 (10.4)	0.001
PDA ligation	3 (27.3)	2 (10.7)	9 (13.4)	0.159
Necrotizing enterocolitis	3 (27.3)	7 (12.5)	10 (14.9)	0.349
Sepsis	3 (27.3)	19 (33.9)	22 (32.8)	0.742
Death	3 (27.3)	4 (7.1)	7 (10.4)	0.081

Values are presented as number (%) and median (range). PH: pulmonary hypertension, C-section: Cesarean section, PROM: premature rupture of membranes, NICU: neonatal intensive care unit, CPAP: continuous positive airway pressure, PDA: patent ductus arteriosus

onitis, oligohydramnios, polyhydramnios, or preeclampsia. The symptomatic early PH group showed significantly lower median 1-min and 5-min Apgar scores than the no PH group ($p = 0.001$ for both). The median duration of ventilator care was significantly longer in the symptomatic early PH group than in the no PH group ($p < 0.001$), whereas the admission duration in NICU and the duration of oxygen use were not significantly different between the two groups. During hospitalization, the symptomatic early PH group had a significantly higher incidence of intraventricular hemorrhage (IVH) and pulmonary hemorrhage than the no PH group ($p = 0.043$ and $p = 0.001$, respectively). There was no significant difference in other complications including necrotizing enterocolitis, retinopathy of prematurity, sepsis, and death.

Among the 67 patients, 25 had mild BPD, 4 had moderate BPD, 9 had severe BPD, and 22 had no BPD. Seven patients died before postnatal day 28 so BPD could not be defined in these patients. The incidence of symptomatic early PH was highest in severe BPD, although this was not statistically significant (4.5% in no BPD, 16% in mild BPD, 0% in moderate BPD, and 33.3% in severe BPD) (Fig. 1).

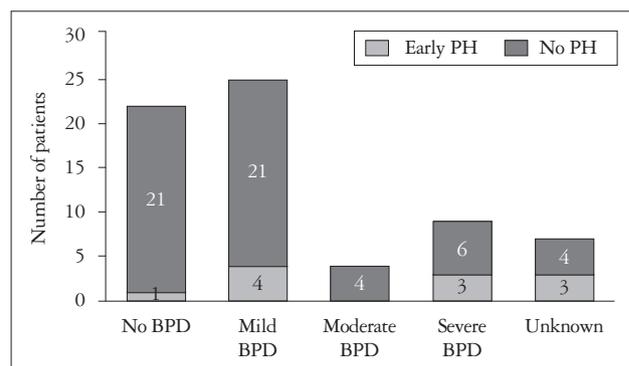


Fig. 1. Incidence of early PH and BPD severity. The incidence of symptomatic early PH was highest in severe BPD. BPD: bronchopulmonary dysplasia, PH: pulmonary hypertension.

ECHOCARDIOGRAPHIC FINDINGS

Echocardiographic parameters by symptomatic early PH status are shown in Table 2. First echocardiography was performed a median 5 days after birth (range, 2–14 days). Although TR jet was found in all patients, only 19 patients (28.4%) including 4 in the symptomatic early PH group and 15 in the no PH group had moderate to severe TR, which could be measured

proper peak velocity. The other patients with trivial and mild TR did not presented adequate Doppler wave. The mean systolic EI of the symptomatic early PH group was significantly lower than that of the no PH group ($p = 0.022$). The mean RV MPI value was higher in the symptomatic early PH group than in the no PH group with no significant difference, but the percentage of patients with an RV MPI > 0.38 in the symptomatic early PH group was significantly higher than that in the no PH group ($p = 0.042$). The mean TAPSE value was not significantly lower in the symptomatic early PH group than in the no PH group, but the percentage of patients with a TAPSE < 0.5 cm in the symptomatic early PH group was significantly higher than that in the no PH group ($p = 0.046$). A

second echocardiography was performed a median 41 days after birth (range, 22–64 days) in 37 patients. No significant difference was found in second echocardiography between groups except for the mean systolic EI, which was significantly lower in the symptomatic early PH group than in the no PH group ($p = 0.023$).

Echocardiographic parameters by BPD severity are summarized in Table 3. TR jet was found in 16 patients (26.7%); 6 with no BPD, 5 with mild BPD, and 5 with severe BPD. Among patients with or without BPD, there was no significant intergroup difference in first echocardiography. In the second echocardiography, the mean RV MPI of patients with severe BPD was significantly higher than that of patients with

Table 2. Echocardiographic parameters according to early PH

Variables	First echocardiograms*			Second echocardiograms†		
	Early PH	No PH	<i>p</i> value	Early PH	No PH	<i>p</i> value
Number	11	56		6	31	
TR	2.44 ± 0.23	2.35 ± 0.68	0.790	2.76 ± 0.20	None	Not available
TR > 3.2 m/sec velocity	0	2 (14.3)	0.685	None	None	Not available
RV MPI	0.46 ± 0.16	0.34 ± 0.21	0.076	0.35 ± 0.23	0.22 ± 0.15	0.080
RV MPI > 0.38	8 (72.7)	20 (35.7)	0.042	2 (33.3)	5 (16.1)	0.571
EI (systole)	0.67 ± 0.14	0.76 ± 0.11	0.022	0.75 ± 0.12	0.85 ± 0.08	0.023
EI (systole) < 0.81	9 (81.8)	34 (60.7)	0.304	5 (83.3)	12 (38.7)	0.075
EI (diastole)	0.68 ± 0.04	0.76 ± 0.14	0.098	0.80 ± 0.06	0.83 ± 0.08	0.320
EI (diastole) < 0.81	11 (100.0)	42 (75.0)	0.103	3 (50.0)	14 (45.2)	0.828
TAPSE	0.48 ± 0.08	0.54 ± 0.10	0.075	0.72 ± 0.08	0.82 ± 0.16	0.139
TAPSE < 0.5 cm	8 (72.7)	21 (37.5)	0.046	None	None	Not available
FS	38.3 ± 6.5	34.1 ± 6.3	0.053	38.9 ± 9.4	37.1 ± 7.5	0.628

Values are presented as number (%) and mean ± standard deviation. *TR peak velocity was measured in 4 patients in PH group and 15 in no PH group, †TR peak velocity was measured in 2 patients in PH group. PH: pulmonary hypertension, TR: tricuspid regurgitation, RV MPI: right ventricle myocardial performance index, EI: eccentricity index, TAPSE: tricuspid annular plane systolic excursion, FS: fractional shortening

Table 3. Echocardiographic parameters according to BPD

Variables	First echocardiograms*				Second echocardiograms†			
	No BPD	Mild BPD	Moderate BPD	Severe BPD	No BPD	Mild BPD	Moderate BPD	Severe BPD
Number	22	25	4	9	11	14	2	9
TR	2.68 ± 0.82	1.87 ± 0.29	None	2.34 ± 0.13	None	None	None	2.76 ± 0.20
TR > 3.2 m/sec velocity	2 (9.1)	0	0	0	0	0	0	0
RV MPI	0.32 ± 0.19	0.33 ± 0.18	0.20 ± 0.06	0.48 ± 0.28	0.24 ± 0.11	0.15 ± 0.07	0.27 ± 0.09	0.37 ± 0.24‡
RV MPI > 0.38	8 (36.4)	9 (36.0)	0 (0)	6 (66.7)	2 (18.2)	0 (0)	0 (0)	4 (44.4)‡
EI (systole)	0.77 ± 0.12	0.74 ± 0.11	0.76 ± 0.13	0.81 ± 0.08	0.88 ± 0.08	0.82 ± 0.11	0.93 ± 0.08	0.79 ± 0.06§
EI (systole) < 0.81	12 (54.5)	17 (68.0)	2 (50.0)	4 (44.4)	2 (18.2)	7 (50.0)	0 (0)	7 (77.8)§
EI (diastole)	0.76 ± 0.19	0.75 ± 0.10	0.72 ± 0.10	0.77 ± 0.09	0.83 ± 0.07	0.82 ± 0.08	0.79 ± 0.04	0.84 ± 0.09
EI (diastole) < 0.81	19 (86.4)	16 (64.0)	3 (75.0)	6 (66.7)	4 (36.4)	5 (35.7)	2 (100.0)	5 (55.6)
TAPSE	0.56 ± 0.11	0.53 ± 0.07	0.55 ± 0.19	0.51 ± 0.12	0.86 ± 0.12	0.82 ± 0.13	0.64 ± 0.02	0.78 ± 0.19
TAPSE < 0.5 cm	7 (31.8)	10 (40.0)	2 (50.0)	3 (33.3)	0	0	0	0
FS	33.8 ± 7.4	34.5 ± 5.43	32.1 ± 2.0	37.8 ± 7.9	33.5 ± 5.5	36.1 ± 7.2	40.3 ± 1.2	44.1 ± 9.1

Values are presented as number (%) and mean ± standard deviation. *TR peak velocity was measured in 6 patients in no BPD, 5 in mild BPD, and 5 in severe BPD, †TR peak velocity was measured in 2 patients in severe BPD, ‡ $p < 0.05$ vs. mild BPD, § $p < 0.05$ vs. no BPD. BPD: bronchopulmonary dysplasia, TR: tricuspid regurgitation, RV MPI: right ventricle myocardial performance index, EI: eccentricity index, TAPSE: tricuspid annular plane systolic excursion, FS: fractional shortening

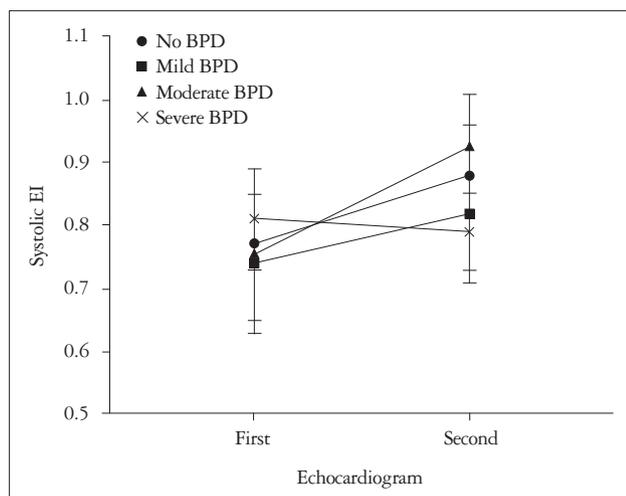


Fig. 2. The serial changes of systolic EI in patients without BPD or with mild, moderate, and severe BPD. Values represent as mean with standard deviation. EI: eccentricity index, BPD: bronchopulmonary dysplasia.

mild BPD ($p = 0.026$), and the mean systolic EI of patients with severe BPD was significantly lower than that of patients with no BPD ($p = 0.034$). Correspondingly, the percentage of patients with an RV MPI > 0.38 in the severe BPD group was significantly higher than that in the mild BPD ($p = 0.014$). Further, a significantly higher percentage of patients with severe BPD had a systolic EI < 0.81 compared to patients without BPD ($p = 0.022$). The mean systolic EI of patients with severe BPD showed a mild decrease in the second echocardiography, in contrast to other patients with increase (Fig. 2). The development of BPD according to first echocardiographic parameters was evaluated. However there was no significant difference in BPD severity according to RV MPI > 0.38 , EI < 0.81 , or TAPSE < 0.5 cm in first echocardiogram.

DISCUSSION

In this study, we found that TR peak velocity was properly measured in a small proportion of patients (28.4%) and systolic EI, RV MPI, and TAPSE were well represented symptomatic early PH. Moreover, systolic EI and RV MPI could be useful parameters for identifying late PH in preterm infants with BPD, even if they did not present with PH symptoms. But in this study, the incidence of symptomatic early PH and early echocardiographic parameters were not associated with the development of BPD.

PH associated with BPD is caused by the impaired vascular growth and function that results from pre- and postnatal injuries and develops mainly in the preterm infants.⁵ Many preterm survivors complicated by BPD are at risk of developing secondary PH and this is called late PH commonly diagnosed over 36 weeks PMA. The incidence of late PH in infants with BPD was 25–37%, and PH contributes to the high mortality (40–47%) of patients with BPD.^{11–13} Some preterm infants with delayed pulmonary transition after birth showed persistent PH

within 2 weeks and this is called early PH.¹ Few studies reported the incidence of early PH and its clinical implications for BPD or late PH. Mirza et al.² reported that the incidence of early PH at 10–14 days of life was 8% of premature infants < 28 weeks and early PH was associated with a greater risk for moderate/severe BPD or death. And during the serial follow-up, all cases of early PH were resolved except one case.¹⁴ Mourani et al.¹⁵ showed that the incidence of early PH at 7 days of age was 42% and late PH at 36 weeks PMA was 14% of preterm infants with birth weights 500–1250 g. Also, they reported that early PH was associated with the development of BPD in preterm infants. In the present study, the incidence of symptomatic early PH in preterm neonates < 30 weeks' gestation was 16.4% and the incidence of BPD in preterm neonates < 30 weeks' gestation was 56.7% (37.3% in mild BPD, 6.0% in moderate BPD, and 13.4% in severe BPD). Unlike the previous studies, the incidence of symptomatic early PH was not significantly associated with BPD development. Although the incidence of symptomatic early PH was highest in severe BPD, this was not statistically significant.

Many studies found that the risk factors for developing late PH in preterm infants are low birth weight, low Apgar scores, oligohydramnios, pulmonary hypoplasia, PROM, prolonged mechanical ventilation and oxygen supplementation, and a PDA requiring surgical correction.^{11,16} However, only one cohort study demonstrated the clinical findings in early PH. It showed that infants with early PH had a prolonged need for mechanical ventilation and greater supplemental oxygen.² We also found that low gestational age and birth weight, low 1-min and 5-min Apgar scores, long duration of ventilator care, and high incidence of IVH and pulmonary hemorrhage are related with symptomatic early PH.

Echocardiography is an important tool in the assessment of PH and RV function in preterm infants with BPD.^{6,17} The most commonly used parameter to determine RV systolic pressure is TR peak velocity, which reflects sPAP in the absence of RV outflow obstruction. However, the identification of TR peak velocity is usually difficult in BPD patients, and it may not be reliable due to associated pulmonary hyperinflation and alteration of cardiac position.¹⁸ Several studies showed an incidence of TR detection of 14–80%.^{19,20} Also in the present study, TR peak velocity was properly measured in a small proportion of patients, only 19 of the total number of enrolled patients (28.4%), and only 10 patients (26.3%) with BPD. If TR was not quantifiable, RV S/D ratio, InT and DT of pulmonary flow, TAPSE, EI, and PD-derived MPI or TDI-derived MPI, etc. can be used to assess sPAP and RV dysfunction. The IVS position is commonly used to assess RV systolic pressure in preterm infants. IVS flattening is seen as a D-shaped LV, and it can be quantified by the EI.⁵ One study in extremely low-birth-weight infants showed that systolic EI and diastolic EI values were significantly lower in the BPD with PH group than in the BPD only group. As such, they recommended the use of EI as a useful

screening tool for PH in extremely low-birth-weight infants.²¹⁾ RV hypertrophy and global function are important to PH outcome and MPI (PD- and TDI-derived) is a quantitative measure of global systolic and diastolic ventricular function.²²⁾ Several studies showed that TDI- and PD-derived MPI were higher in the BPD group than in the control and was noted to correlate with BPD severity.²³⁾²⁴⁾ TAPSE is most easily used to measure longitudinal RV lateral wall performance, which correlates with RV ejection fraction.⁶⁾ TAPSE was linearly increased as gestational age in preterm neonates and was significantly lower in PH patients.¹⁰⁾²⁵⁾ Also, this study demonstrated that patients with symptomatic early PH showed a significantly lower systolic EI and a significantly higher incidence of RV MPI > 0.38 and TAPSE < 0.5 cm than patients without early PH. Patients with severe BPD showed a significantly higher RV MPI and a significantly higher incidence of RV MPI > 0.38 than patients with mild BPD, and a significantly lower systolic EI and a significantly higher incidence of systolic EI < 0.81 than patients without BPD. Although measuring these parameters would take longer time of examination and more stress to preterm infant, systolic EI, RV MPI, and TAPSE may be more sensitive for identifying PH, especially in preterm infants with BPD without PH symptoms than TR peak velocity, right-to-left shunt or IVS flattening.

In studies about early PH and BPD, septal flattening at 7 days of age was strongly associated with the development of BPD,¹⁵⁾ and the PD-derived RV MPI was higher in very low birth weight infants with BPD than in those without BPD between 7 and 28 days of life.²⁶⁾ These findings suggest that the elevated RV pressure in first week after birth may affect early pulmonary vascular injury and increases risk for BPD. We also evaluated the development of BPD according to first echocardiographic parameters. However there was no significant difference in BPD severity on the basis of RV MPI > 0.38, EI < 0.81, or TAPSE < 0.5 cm.

The relation between early and late PH remains unclear. One study reported that most early PH were resolved during follow-up, whereas the other study reported that early PH (septal wall flattening and RV dilation) was associated with late PH in preterm infants.¹⁴⁾¹⁵⁾ In the present study, we found that the patients with symptomatic early PH had persistently lower mean systolic EI in both first and second echocardiograms. However as mentioned above, the mean systolic EI was not correlated with the BPD development.

There are some limitations to this study. First, we enrolled a small number of preterm infants in a single-center study. Second, TR velocity was evaluated in small part of patients because most patients showed too small amount of TR to detect adequate peak velocity. Third, the time of echocardiograms had a wide range and only approximately 50% of enrolled patients underwent secondary echocardiograms due to patients' clinical situations. We did not performed long-term follow up echocardiogram in patients with BPD to assess changes in PH. Forth,

we did not classified the PH by severity (mild, moderate, and severe), nor did we determined the relation between PH severity and BPD.

In conclusion, our study revealed that systolic EI, RV MPI, and TAPSE were useful parameters for identifying early and late PH. In addition, it showed the incidence of symptomatic early PH and early echocardiographic parameters were not associated with the development of BPD. This means that the risk of BPD cannot be predicted by only one time echocardiogram in early life of preterm infants. Actually, the optimal timing for screening for PH in preterm infants has not been determined. We think that the serial follow-up echocardiographic screening is important for identifying PH prior to prominent clinical symptoms.

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