의학석사 학위논문

Long-term outcomes of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia

기관지폐이형성증이 있는 미숙아에서 발생한 폐동맥 고혈압의 장기 결과

2016년 2월

서울대학교 대학원

임상의과학과 임상의과학전공

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이 논문을 의학석사 학위논문으로 제출함

2015년 10월

서울대학교 대학원

임상의과학과 임상의과학전공

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권혜원의 의학석사 학위논문을 인준함

2016년 1월

위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

Long-term outcomes of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia

by

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A Thesis Submitted to the Department of Clinical Medical Sciences in Partial Fulfillment of the Requirements for the Degree of Master of Science in Clinical Medical Sciences at the Seoul National University College of Medicine

January, 2016

Approved by thesis committee:

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ABSTRACT

Background: Infants with bronchopulmonary dysplasia (BPD) are known to have a high risk of pulmonary hypertension (PH). However, the long-term outcomes of PH in preterm infants with BPD are uncertain. The purpose of this study was to assess outcomes of PH in prematurely born children diagnosed with moderate to severe BPD.

Methods: We retrospectively reviewed medical records of patients born before 32 weeks' gestation and diagnosed with moderate to severe BPD from June 2004 to April 2008. Patients were recruited for a cross-sectional study from August to October 2014 and underwent an echocardiography.

Results: Forty-two children were enrolled. Their mean gestational age and birth weight were 26.2 ± 1.7 weeks and 753.1 ± 172.5 g, respectively. Sixteen patients (38%) were diagnosed with PH at a mean age of 3.3 ± 1.6 months, and the PH was improved after a median 12.3 months (range 0.7-46.6 months). Cardiovascular function was reassessed at a mean age of 7.7 ± 0.9 years, at which time 1 patient had been taking a medication for recurrent PH. Conventional two-dimensional and Doppler echocardiography indicated normal ventricular function in all children. However, right ventricular global longitudinal strains decreased in children with previous PH.

Conclusions: Subclinical ventricular dysfunction was detectable using

sensitive echocardiographic techniques in children with previous BPD-associated PH. Long-term follow-up and meticulous cardiovascular functional assessment is required in this population.

Key words: Pulmonary hypertension, Bronchopulmonary dysplasia, Premature infants

Student number: 2013-22595

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List of abbreviations and symbols

BPD: bronchopulmonary dysplasia

PH: pulmonary hypertension

PA: pulmonary artery

RV: right ventricle (ventricular)

TDI: tissue Doppler imaging

STE: speckle-tracking echocardiography

SNUH: Seoul National University Hospital

NICU: neonatal intensive care unit

FiO_2: fraction of inspired oxygen

TR: tricuspid regurgitation

BP: blood pressure

LV: left ventricle (ventricular)

FS: fractional shortening

EF: ejection fraction

E velocity: early diastolic transmitral flow velocity

A velocity: late diastolic transmitral flow velocity during atrial contraction

E/A ratio: ratio of early to late diastolic transmitral flow velocity

TAPSE: tricuspid annular plane systolic excursion

FAC: fractional area change

PR: pulmonary regurgitation

PVR: pulmonary vascular resistance

TRV/TVI_{RVOT}: ratio of peak tricuspid regurgitation velocity to right ventricular outflow tract velocity time integral

AcT: flow acceleration time

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that follows the use of ventilator and oxygen therapy for neonatal respiratory failure in preterm infants [1]. In addition to adverse effects on the airway, acute lung injury after premature birth also impairs growth, structure, and function of the developing lung circulation [2]. Early injury to the lung circulation leads to the rapid development of pulmonary hypertension (PH), which contributes to significant morbidity and mortality in infants with BPD [2, 3]. However, the long-term outcomes of PH in BPD survivors remain uncertain.

Long-term increases in pulmonary arterial (PA) pressure may lead to changes in right ventricular (RV) geometry, structure, and function, a process known as cardiac remodeling [4, 5]. Even though conventional echocardiography, such as two-dimensional and Doppler echocardiography, has been used to evaluate ventricular function as well as to estimate PA pressure non-invasively, the conventional methods do not provide sensitive markers of ventricular remodeling [6]. Advanced cardiac imaging of the ventricle, including with tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE), can provide quantitative information that often precedes the information provided by conventional method [7].

The purpose of this study was to assess outcomes of PH in prematurely

born children diagnosed with moderate to severe BPD. In this study, we performed TDI and STE in addition to conventional echocardiography to identify sensitive markers of ventricular remodeling.

Subjects and Methods

Study Protocol

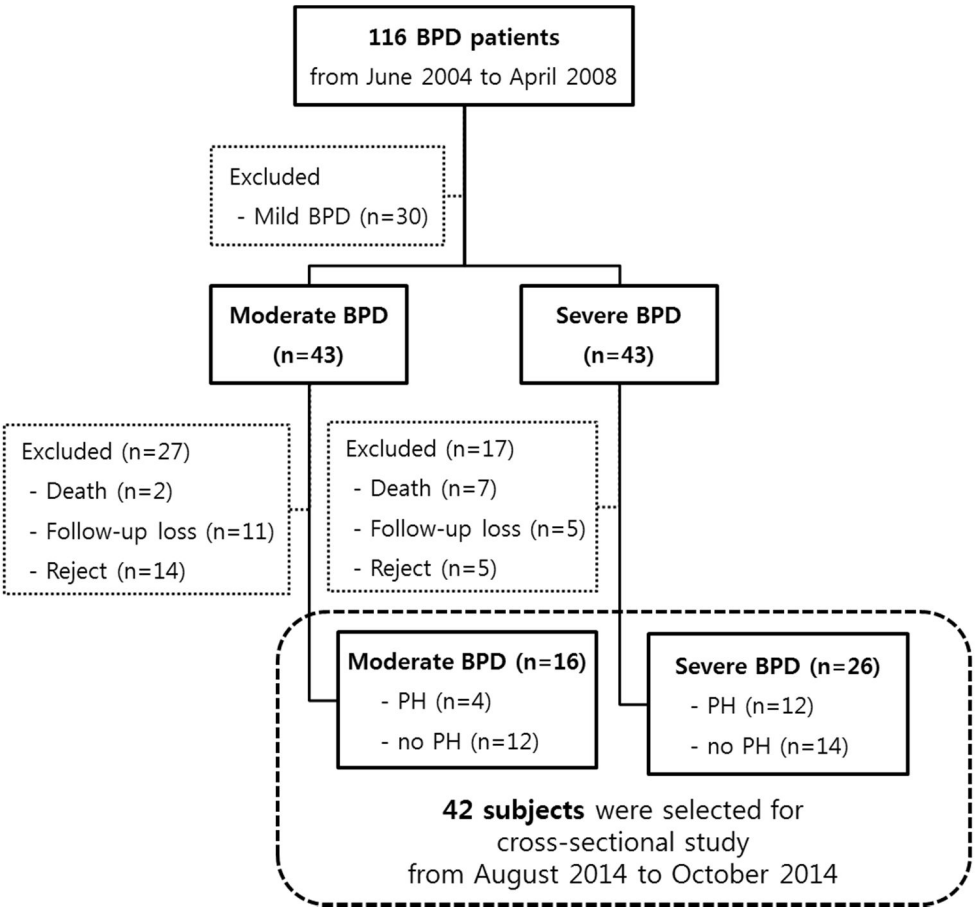
This study comprised a retrospective analysis of clinical data and a cross-sectional, non-invasive investigation of cardiovascular function. Written informed consent was obtained from all parents and most children who could understand the study protocol and write their names. This study complied with the Declaration of Helsinki, and approval for its conduct was provided by the Ethics Committee of Seoul National University Hospital (SNUH).

Study Participants

From June 2004 to April 2008, 116 patients were diagnosed with BPD at the SNUH, as reported in our previous study [8]. Among them, 30 with mild BPD were excluded from the present study because none exhibited evidence of PH during treatment in the neonatal intensive care unit (NICU) [8]. Nine patients died before this cross-sectional study; 5 with severe BPD and PH died at average 6.8 months (range 3–14 months) of chronologic age because of respiratory failure during NICU admission, 2 with severe BPD without PH died due to respiratory infection after NICU discharge at 6 and 17 months of age, respectively, and 2 with moderate BPD without PH died at 3 months and 7 years of age because of sepsis and unknown cause, respectively.

Patients who were lost to follow-up (16 patients), or refused to participate in the study (19 patients) were also excluded. The remaining 42 subjects (16 with moderate BPD and 26 with severe BPD) were selected for cross-sectional study (Figure 1).

Figure 1. Flow diagram of the study design and the 42 patients with bronchopulmonary dysplasia



BPD: bronchopulmonary dysplasia, PH: pulmonary hypertension

Retrospective Study

We reviewed patients' clinical data from medical records, including sex, gestational age at birth, birth weight and length, duration of oxygen use, duration of ventilator support, and ventilator mode. BPD was defined as oxygen treatment for ≥28 days, and its severity was graded as follows: mild BPD, breathing room air; moderate BPD, requiring a <30% fraction of inspired oxygen (FiO_2); severe BPD, requiring ≥30% FiO_2 and/or positive pressure support at 36 weeks of age [1]. Diagnosis of PH was made by echocardiography based on the following criteria: 1) a tricuspid regurgitation (TR) velocity ≥3 m/s in the absence of pulmonary stenosis and 2) a flat or left-deviated interventricular septal configuration with RV hypertrophy as previously described [8]. Cases of typical persistent PH of newborns and PH associated with congenital diaphragmatic hernia, meconium aspiration syndrome, or congenital heart disease other than small atrial septal defects, patent foramen ovale, and patent ductus arteriosus.

Cross-sectional Study

The enrolled 42 subjects had visited a cardiovascular center at SNUH between August and October 2014. A single observer measured the subjects'

weights and heights after shoes and all heavy garments were removed. Blood pressure (BP) and heart rate were measured using a Colin BP-S510 patient monitor (DRE, Louisville, KY, USA) after the patient had relaxed comfortably for at least 5 minutes; the average of two measurements was used for analysis. During measurement, the arm was supported at the heart level, and the cuff bladder encircled at least 80% of the arm circumference. Elevated BP was defined as an average systolic BP and/or diastolic BP >95th percentile for sex, age, and height according to normative BP references for Korean children [9].

Echocardiography was performed using a Vivid E9 ultrasound system (GE Healthcare, Little Chalfont, United Kingdom) with a 5-MHz transducer probe. Measurements were taken by a single experienced pediatric cardiologist, and the average of three measurements for each parameter was used for analysis. Both ventricular functional parameters were obtained using indices listed in Table 1 by appropriate measurement respectively. Left ventricular (LV) mass was assessed according to the LV mass-for-height centile curves generated from healthy children [10]. LV functional parameters of systolic function (e.g., fractional shortening [FS], ejection fraction [EF], systolic myocardial velocity at the basal segment of lateral mitral annulus, and LV peak global longitudinal strain), diastolic function

(early diastolic transmitral flow velocity [E velocity], late diastolic transmitral flow velocity during atrial contraction [A velocity], the ratio of early to late diastolic transmitral flow velocity [E/A ratio], and early and late diastolic myocardial velocities at the basal segment of lateral mitral annulus), and global function (LV Tei index) were evaluated. RV functional parameters of systolic function (tricuspid annular plane systolic excursion [TAPSE], fractional area change [FAC], systolic myocardial velocities at the basal segment of lateral tricuspid annulus, and RV peak global longitudinal strain), diastolic function (early and late diastolic myocardial velocities at the basal segment of lateral tricuspid annulus), and global function (RV Tei index) were evaluated according to the guideline of the American Society of Echocardiography [11]. Because we did not have normal control data for myocardial velocities and strain values we compared measured data with normal values for appropriate age groups [12-14]. To estimate PA pressure, peak systolic velocities from TR and pulmonary regurgitation (PR) were measured using continuous-wave Doppler. To estimate pulmonary vascular resistance (PVR), the ratio of peak TR velocity to RV outflow tract velocity time integral (TRV/TVI_{RVOT}) and pulmonary flow acceleration time (AcT) were measured as previously described [15, 16]. In the previous study of adult PH, a TRV/TVI_{RVOT} cutoff value of >0.2 provided a specificity of 94%

and sensitivity of 70% for determining PVR >2 Wood units [15], and a pulmonary AcT cutoff value of <100 ms showed good sensitivity and specificity for detecting mean PA pressures >25 mmHg [16].

Table 1. Functional parameters of echocardiographic examination

1. LV functional parameters

Parameter of LV hypertrophy

- LV mass = $1.04\{(LVSWd+LVIDd+LVPWd)^3-LVIDd^3\}-13.6$*

LV systolic function

- Fractional shortening (FS) = $\{(LVIDd-LVIDs)/LVIDd\} \times 100$*
- Ejection fraction (EF) = $\{(LVIDd^3-LVIDs^3)/LVIDd^3\} \times 100$*
- Systolic myocardial velocities at the basal segment of lateral mitral annulus†
- LV peak global longitudinal strain‡

LV diastolic function

- E velocity: early diastolic transmitral flow velocity
- A velocity: late diastolic transmitral flow velocity during atrial contraction
- E/A ratio=E velocity/A velocity
- Diastolic myocardial velocities at the basal segment of lateral mitral annulus†

LV global function

- LV index of myocardial performance (LV Tei index)= (MCO-AVET)/AVET§

2. Parameters of pulmonary hypertension

Estimated systolic PA pressure : peak systolic velocity from TR

Estimated mean PA pressure : peak systolic velocity from PR

Index of PVR : peak TR velocity/TVI_{RVOT}

Pulmonary flow acceleration time

Ratio of RV/LV dimension ||

3. RV functional parameters

RV systolic function

- Tricuspid annular plane systolic excursion (TAPSE)
- RV fractional area change (FAC) = (RV EDA-ESA/EDA) x 100
- Systolic myocardial velocity at the basal segment of lateral tricuspid annulus†
- RV peak global longitudinal strain‡

RV diastolic function

- Diastolic myocardial velocities at the basal segment of lateral tricuspid annulus†

RV global function

- RV index of myocardial performance (RV Tei index) = (TCO-PVET)/PVET§

LV: left ventricular, LVSWd: LV end-diastolic septal wall thickness, LVIDd: LV end-diastolic internal dimension, LVPWd: LV end-diastolic posterior wall thickness, LVIDs: LV end-systolic internal dimension, MCO: mitral closing time, AVET: aortic ejection time, PA: pulmonary artery, TR: tricuspid regurgitation, PR: pulmonary regurgitation, PVR: pulmonary vascular resistance, TVI: time velocity integral, RVOT: right ventricular outflow tract, RV: right ventricular, EDA: end-diastolic area, ESA: end-systolic area, TCO: tricuspid closing time, PVET: pulmonary ejection time

*LV dimensions were measured in the parasternal long axis using M-mode echocardiography. †Myocardial velocities were measured using pulsed-wave tissue Doppler imaging at the cardiac base in the apical 4-chamber view from two locations: the lateral mitral annulus; and the lateral tricuspid annulus. ‡Two-dimensional speckle tracking echocardiography measured peak systolic longitudinal strain of either ventricle. §To calculate the Tei indices, the time intervals were measured using the myocardial velocities at the at the basal segment of lateral mitral annulus and the lateral tricuspid annulus, respectively. ‖ To estimate the relative RV size, the ratio of the maximal RV dimension to LV dimension was calculated in the basal one-third of the RV and LV on the apical 4-chamber view.

Statistical Analysis

Data were analyzed using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, USA). We compared continuous variables using the Mann–Whitney *U*-test. The chi-squared test or Fisher's exact test was used to evaluate categorical data. A probability value <0.05 was considered significant.

Results

Retrospective Study

The mean gestational age of all subjects was 26.2 ± 1.7 weeks, and the mean birth weight and height were 753.1 ± 172.5 g and 32.5 ± 2.8 cm, respectively. Sixteen patients (34.8%) were diagnosed with PH associated with BPD at a mean chronologic age of 3.3 ± 1.6 months and mean weight of 2.5 ± 1.3 kg. A retrospective comparison of demographics and general characteristics between patients with PH (PH group) and without PH (non-PH group) is presented in Table 2. The PH group had a significantly lower birth weight and length than the non-PH group, as well as longer oxygen and ventilator treatment durations and higher maximal peak inspiratory pressure and peak end-expiratory pressure during ventilator support. Although severe BPD was also more prevalent in the PH group, this difference was not statistically significant. Echocardiography during NICU admission revealed a significantly higher TR peak velocity in the PH group than in the non-PH group (3.57 ± 0.62 m/s versus 2.44 ± 0.51 m/s; P <0.0001).

Table 2. Demographics and clinical characteristics between subjects with and without previous pulmonary hypertension from retrospective study

	Total (N = 42)	PH (N = 16)	Non-PH (N = 26)	*P*-value
Male (n)	29 (69.0%)	12 (75.0%)	17 (65.4%)	0.733
Gestational age (wk)	26.2 ± 1.7	26.2 ± 2.1	26.2 ± 1.4	0.625
Birth weight (g)	753.1 ± 172.5	689.7 ± 189.4	790.7 ± 122.5	0.026
Birth height (cm)	32.5 ± 2.8	31.1 ± 2.7	33.3 ± 2.1	0.003
Apgar score at 1 minute	3.4 ± 1.68	3.1 ± 1.45	3.6 ± 1.84	0.335
Apgar score at 5 minutes	5.5 ± 1.52	4.9 ± 1.75	6.0 ± 1.20	0.050
Duration of oxygen use (d)	181.1 ± 152.42	288.8 ± 196.65	115.5 ± 57.01	0.001
Conventional ventilator (d)	44.3 ± 29.35	62.4 ± 30.27	34.3 ± 24.17	0.008
High frequency ventilator (d)	5.0 ± 9.39	9.5 ± 12.40	1.2 ± 2.46	0.003
Inhaled nitrogen oxide (d)	3.6 ± 9.48	9.1 ± 13.88	0.1 ± 0.64	< 0.001
Nasal CPAP (d)	23.5 ± 17.49	25.4 ± 21.94	22.7 ± 14.72	0.836
Maximal PIP (mmHg)	19.9 ± 5.84	23.8 ± 5.13	17.3 ± 5.13	< 0.001
Maximal PEEP (mmHg)	6.5 ± 1.78	7.6 ± 2.19	5.9 ± 1.17	0.004
Severe BPD (n)	26 (61.9%)	12 (75.0%)	14 (53.8%)	0.170

Steroid for BPD (n)	10 (23.8%)	7 (43.8%)	3 (11.5%)	0.027
RDS (n)	29 (69.0%)	13 (81.3%)	16 (61.5%)	0.303
PDA (n)	35 (83.3%)	12 (75.0%)	23 (88.5%)	0.397
Maximal size of PDA (mm)	2.08 ± 0.61	2.42 ± 0.81	1.92 ± 0.45	0.143
Duration of PDA (d)	29.5 ± 91.1	58.7 ± 163.1	22.5 ± 37.8	0.464
ASD or PFO (n)	34 (81.0%)	15 (93.8%)	19 (73.1%)	0.127
Maximal TR peak velocity (m/s)	2.95 ± 0.79	3.57 ± 0.62	2.44 ± 0.51	<0.001

Continuous variables are expressed as means ± standard deviations.

PH: pulmonary hypertension, CPAP: continuous positive airway pressure, PIP: peak inspiratory pressure, PEEP: positive end-expiratory pressure, BPD: bronchopulmonary dysplasia, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, ASD: atrial septal defect, PFO: patent foramen ovale, TR: tricuspid regurgitation

Ten patients in the PH group (62.5%) were treated with a pulmonary vasodilator, sildenafil, for an average of 17.5 ± 16.3 months (range: 1.1–47.3 months). The mean chronologic age and weight at the start of treatment were 4.0 ± 2.2 months and 2.9 ± 1.4 kg, respectively. Sildenafil was initiated at an average dosage of 1.0 ± 0.6 mg/kg/d (range: 0.51–2.01 mg/kg/d), and was increased to 3.0 ± 1.8 mg/kg/d (range: 1.01–7.04 mg/kg/d). We could not find cardiovascular complications such as hypotension or flushing in the patient who had sildenafil treatment. Among sildenafil-treated patients, normalization of TR peak velocity and RV morphology was achieved after an average interval of 18.0 ± 15.4 months (median: 17.7 months, range: 2.3–46.6 months) from diagnosis of PH and at a mean chronologic age of 21.2 ± 14.4 months (median: 21.7months, range: 3.9–47.3 months). One patient experienced recurrent PH at 43 months after sildenafil discontinuation and began treatment with another pulmonary vasodilator, bosentan, at the age of 6.8 years.

Although six patients in the PH group did not receive pulmonary vasodilator treatment, they exhibited improved PH after an average interval of 7.8 ± 6.7 months (median: 8.1 months, range: 0.7–16.2 months) from diagnosis of PH and at a mean chronologic age of 10.3 ± 6.7 months (median: 10.9 months, range: 2.6–17.4 months). The mean TR peak velocity during

NICU admission was higher among pulmonary vasodilator-treated patients than that among untreated patients, although this difference was not statistically significant (3.70 ± 0.63 m/s versus 3.13 ± 0.40 m/s; $P = 0.147$; data not shown).

Cross-sectional Study

The mean chronologic age at the time of the cross-sectional study was 7.7 ± 0.9 years (range: 6.4–10.2 years). The mean weight and height were 21.9 ± 5.2 kg and 120.1 ± 7.6 cm, respectively. Elevated BP in hypertensive range was identified in 12 patients (28.6%); their mean systolic and diastolic BPs were 118.5 ± 7.9 mmHg and 71.7 ± 13.6 mmHg, respectively. Elevated BP was identified more frequently in the PH group than it was in the non-PH group (50% versus 15.4%; $P = 0.032$) (Table 3). In the univariate analysis, previous PH showed a significant correlation with elevated BP (odds ratio, 5.50; $P = 0.021$). Severity of BPD, steroid treatment for BPD, and hydrocortisone administration for adrenal insufficiency showed no correlation with increased BP. Multivariate analysis showed no significant associations between elevated BP and any of the factors studied (data not shown).

The results of the LV functional study are shown in Table 3. No subject had

an LV mass-for-height above the 95th percentile. There was no significant difference in the LV mass index, FS, EF, E/A ratio, LV Tei index, myocardial velocities at lateral mitral annulus, and LV peak global longitudinal strain between the PH and non-PH groups.

Table 3. Clinical characteristics and echocardiographic assessment of left ventricular function between subjects with and without previous pulmonary hypertension from cross-sectional study

	Total (N = 42)	PH (N = 16)	Non-PH (N = 26)	*P*-value
Clinical characteristics				
Age (y)	7.7 ± 0.9	7.6 ± 1.1	7.7 ± 0.8	0.491
Body weight (kg)	21.9 ± 5.2	23.1 ± 6.1	21.2 ± 4.6	0.534
Height (cm)	120.1 ± 7.6	119.0 ± 7.6	120.8 ± 7.6	0.260
BSA (m^2)	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.679
Systolic BP (mmHg)	112.4 ± 8.0	114.7 ± 9.6	111.0 ± 6.7	0.139
Diastolic BP (mmHg)	61 ± 11.5	59.4 ± 9.9	62.1 ± 12.4	0.765
Elevated BP* (n)	12 (28.6%)	8 (50%)	4 (15.4%)	0.032
Pulse rate (bpm)	89.0 ± 11.3	90.2 ± 10.3	88.3 ± 12.1	0.641
LV mass and dimensions				
LV mass (g)	49.50 ± 10.37	49.05 ± 10.70	49.77 ± 10.36	0.846
LVIDd (mm)	35.43 ± 2.81	35.07 ± 2.95	35.65 ± 2.75	0.392
LVIDs (mm)	21.76 ± 2.33	21.50 ± 2.52	21.91 ± 2.24	0.452
LV systolic function				
LV FS (%)	38.59 ± 4.1	38.70 ± 4.08	38.52 ± 4.19	0.660

LV EF (%)	69.70 ± 5.03	69.88 ± 5.13	69.58 ± 5.06	0.660
LV lateral S' (cm/s)	7.7 ± 1.8	7.3 ± 1.8	7.9 ± 1.8	0.170
LV longitudinal strain (%)	- 22.44 ± 4.31	-22.08 ± 6.50	-22.66 ± 2.22	0.319
LV diastolic function				
E velocity (m/s)	0.99 ± 0.14	1.01 ± 0.17	0.98 ± 0.13	0.622
A velocity (m/s)	0.58 ± 0.11	0.60 ± 0.11	0.56 ± 0.11	0.218
E/A ratio	1.81 ± 0.54	1.75 ± 0.54	1.85 ± 0.55	0.543
LV lateral E' (cm/s)	14.4 ± 3.1	13.4 ± 2.3	15.0 ± 3.5	0.203
LV lateral A' (cm/s)	6.0 ± 1.3	6.0 ± 1.4	6.0 ± 1.3	0.925
LV global function				
LV Tei index	0.32 ± 0.05	0.31 ± 0.05	0.33 ± 0.05	0.208

Results are expressed as means ± standard deviations.

PH: pulmonary hypertension, BSA: body surface area, BP: blood pressure, LV: left ventricular, LVIDd: left ventricular end-diastolic internal dimension, LVIDs: left ventricular end-systolic internal dimension, FS: fractional shortening, EF: ejection fraction, LV lateral S': systolic myocardial velocity at the basal segment of lateral mitral annulus, E velocity: early diastolic transmitral flow velocity, A velocity: late diastolic transmitral flow velocity during atrial contraction, LV lateral E': early diastolic myocardial velocity at the basal segment of lateral mitral annulus, LV lateral A': late diastolic

myocardial velocity at the basal segment of lateral mitral annulus

* Elevated BP was defined as an average systolic BP and/or diastolic BP >95th percentile for sex, age, and height according to normative BP references for Korean children [8].

The results of the indirect PH markers and RV functional study are shown in Table 4. TR peak velocity measurement was possible in 31 patients; the mean value was 2.41 ± 0.27 m/s, with a TRV/TVI_{RVOT} of 0.14 ± 0.03. Trivial PR was detected in 19 patients; the mean PR peak velocity was 1.61 ± 0.37 m/s, which was within the normal range. Pulmonary AcT was lower in the PH group than in the non-PH group, with borderline significance (105.40 ± 20.77 versus 119.69 ± 21.79; $P = 0.053$). All patients had a normal RV size and interventricular septal configuration. There were no significant differences in the TR peak velocity, TAPSE, RV Tei index, and myocardial velocities at lateral tricuspid annulus between the PH and non-PH groups. However, RV global longitudinal strain was significantly lower in the PH group than in the non-PH group (-24.25 ± 6.28% versus -28.45 ± 4.26%; $P = 0.020$). Although RV FAC showed significant difference between two groups, the absolute values in the both groups were normal according to a previous study [17].

Table 4. Echocardiographic parameters for pulmonary hypertension and assessment of right ventricular function between subjects with and without previous pulmonary hypertension from cross-sectional study

	Total (N = 42)	PH (N = 16)	Non-PH (N = 26)	*P*-value
Parameters of pulmonary hypertension				
TR peak velocity (m/s)	2.41 ± 0.27 (N=31)	2.51 ± 0.22 (N=12)	2.36 ± 0.29 (N=19)	0.084
PR peak velocity (m/s)	1.61 ± 0.37 (N=19)	1.75 ± 0.40 (N=11)	1.42 ± 0.23 (N=8)	0.047
TRV/TVI_{RVOT}	0.14 ± 0.03 (N=31)	0.15 ± 0.03 (N=12)	0.14 ± 0.03 (N=19)	0.389
Pulmonary AcT (ms)	114.24 ± 22.29	105.40 ± 20.77	119.69 ± 21.79	0.053
Ratio of RV/LV dimension	0.73 ± 0.08	0.74 ± 0.09	0.72 ± 0.08	0.650
RV systolic function				
TAPSE (mm)	18.8 ± 2.9	18.4 ± 4.0	19.0 ± 2.0	0.517
RV FAC (%)	46.03 ± 6.63	42.86 ± 6.42	47.98 ± 6.09	0.018
RV lateral S' (cm/s)	11.7 ± 2.2	11.4 ± 2.2	11.8 ± 2.2	0.656
RV longitudinal strain (%)	- 26.85 ± 5.46	- 24.25 ± 6.28	- 28.45 ± 4.26	0.020

RV diastolic function				
RV lateral E' (cm/s)	15.4 ± 2.8	14.6 ± 3.3	15.8 ± 2.5	0.139
RV lateral A' (cm/s)	9.1 ± 2.3	9.3 ± 2.6	9.0 ± 2.1	0.723
RV global function				
RV Tei index	0.33 ± 0.06	0.33 ± 0.05	0.32 ± 0.07	0.866

Continuous variables are expressed as means ± standard deviations.

PH: pulmonary hypertension, TR: tricuspid regurgitation, PR: pulmonary regurgitation, TRV: peak tricuspid regurgitation velocity, TVI: time velocity integral, RVOT: right ventricular outflow tract, AcT: acceleration time, RV: right ventricular, LV: left ventricular, TAPSE: tricuspid annular plane systolic excursion, FAC: fractional area change, RV lateral S': systolic myocardial velocity at the basal segment of lateral tricuspid annulus, RV lateral E': early diastolic myocardial velocity at the basal segment of lateral tricuspid annulus, RV lateral A': late diastolic myocardial velocity at the basal segment of lateral tricuspid annulus

Discussion

A previous study of school-aged BPD survivors found no evidence of increased PA pressure, as estimated by TR jet velocity, in patients with PH when compared to term and preterm controls without BPD [18]. Recently, Joshi et al. reported that 8–12-year-old survivors of BPD had no subclinical ventricular dysfunction and no evidence of increased PA pressure according to myocardial velocity imaging, even after exposure to hypoxia [19]. In our cross-sectional study, performed in 6-10 year-old survivors of moderate to severe BPD, there were no significant differences in conventional parameters of PH and myocardial velocities between the PH and non-PH groups. However, we observed a significant decrease in the RV longitudinal strain, one of the RV systolic functional parameter, in the PH group relative to those in the non-PH group. STE-estimated RV longitudinal strain has been reported to be an independent predictor of future RV failure, clinical deterioration, and mortality in adult patients with PH [20], and has also recently been used to detect subclinical changes in ventricular function in neonates with PH [7]. RV longitudinal strain might be a sensitive marker of RV remodeling associated with previous PH in children with BPD, even if no abnormalities are observed in conventional parameters of PH. More studies are required to determine whether these parameters would be related to their

exercise capacity or any other morbidity in the future.

BPD-associated PH was reversible in most patients who survived to early childhood from the perspective of conventional echocardiographic parameters of PH, even in those not treated with a pulmonary vasodilator. Sildenafil, a phosphodiesterase type V inhibitor, was the first agent approved by the United States Food and Drug Administration (FDA) for PH treatment in both adults and children. However, in 2014, dose-dependent increases in child mortality led to the withdrawal of the FDA recommendations for the use of sildenafil in pediatric PH [21]. Furthermore, limited evidence exists for the use of sildenafil as a treatment for PH in patients with BPD, and a recent randomized controlled pilot study found that sildenafil treatment did not improve short-term respiratory outcomes [22]. In our retrospective study, the time to normalization of TR peak velocity and RV morphology increased among patients treated with sildenafil relative to that for untreated patients, possibly because patients in the former group had more severe PH. A large, double-blinded, randomized controlled study of the use of pulmonary vasodilators in BPD-associated PH is needed to identify the effectiveness and risks of this agent.

A recent systematic review and meta-analysis showed that children and adults born preterm had higher systolic BP than did those born at term [23],

and the prevalence of systemic hypertension (HTN) among previously preterm school-aged children, adolescents, and adults has been reported as 10–25%, 16%, and 6–10%, respectively [24]. Previous studies have suggested various hypotheses to explain HTN in individuals who were born preterm, including impaired intrauterine kidney growth [25] and accelerated weight gain in the first 36 months of life [26]. In our cross-sectional study, elevated BP in hypertensive range was identified in 28.6% of 6–10-year-old children with previous moderate-to-severe BPD. Interestingly, elevated BP was more prevalent in the patients with previous PH. The higher prevalence of elevated BP in our study relative to that in previous studies might have been due to increased prevalence of BPD-associated PH in our study population. Abman et al. reported that infants with severe BPD and PH have decreased pulmonary vascular clearance or net production of circulating norepinephrine and the study group had a high incidence of PH and HTN [27]. Increased catecholamines and abnormal vasoreactivity in BPD-associated PH could be related to development of HTN. Although further study is required to identify a possible relationship between HTN and previous PH, additional careful follow-up of this population is necessary to screen for the development of HTN.

This study has several limitations primarily due to the lack of a control

group, especially for myocardial tissue Doppler and strain measurements. The observer could not be blinded while obtaining cross-sectional data and selection bias might have occurred because we could not recruit all patients with BPD. Additionally, we did not confirmed elevated BP reading obtained with an oscillometric device by using auscultation and we measured BP on only one occasion. Finally, follow-up was not scheduled uniformly for all patients, precluding us from determining the exact time to resolution of PH.

Conclusion

Although surviving patients with BPD-associated PH can achieve good outcomes in terms of conventional echocardiographic parameters, these children could exhibit subclinical ventricular dysfunction associated with previous PH. Meticulous functional studies of RV that include TDI and STE in addition to conventional echocardiography could be helpful for the early detection of subclinical ventricular dysfunction in patients with previous PH. Elevated BP was not uncommon among children with previous moderate to severe BPD; therefore, long-term follow-up and screening BP measurement are necessary in this population.

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국문초록

배경: 기관지폐이형성증이 있는 미숙아에서 폐동맥 고혈압의 발생 위험이 높다는 것은 알려져 있으나 폐동맥 고혈압의 장기 결과는 잘 알려져 있지 않다. 본 연구에서는 중등도 이상의 기관지폐이형성증을 진단받았던 소아에서 폐동맥 고혈압의 장기간 결과를 평가하고자 하였다.

방법: 서울대학교 어린이병원에서 2004년 6월부터 2008년 4월 사이에 재태연령 32주 미만으로 출생하여 중등도 이상의 기관지폐이형성증을 진단 받은 환자를 대상으로 후향적으로 의무기록을 검토하였다. 이들은 2014년 8월부터 10월까지 단면조사연구를 위해 모집되어 심장 초음파 검사를 시행하였다.

결과: 42명의 환자가 참여하였으며, 이들의 재태연령은 26.2 ± 1.7 주, 출생 체중은 753.1 ± 172.5 g 이었다. 42명 중 16명(38%)의 환자가 평균 3.3 ± 1.6 개월에 폐동맥 고혈압을 진단받았으며, 폐동맥 고혈압이 진단된 후 호전될 때까지 걸린 시간의 중위값은 14.2 개월(범위, 0.7-46.6 개월)이었다. 심혈관계의 기능에 대한 단면조사 연구는 평균 7.7 ± 0.9 세에 시행되

었으며, 연구 당시에 1명의 환자가 재발한 폐동맥 고혈압으로 약물을 복용하고 있었다. 고식적인 이면상과 도플러 심장 초음파 검사 결과, 모든 대상자에서 심실의 기능은 정상으로 측정되었으나 이전에 폐동맥 고혈압을 진단 받았던 환자에서는 우심실의 최고 전 세로 긴장도가 감소되어 있었다.

결론: 이전에 기관지폐이형성증과 관련된 폐동맥 고혈압이 있었던 소아에서는 민감한 심장 초음파 검사 방법으로 잠복성의 심실 기능의 이상을 발견할 수 있었다. 따라서 이러한 소아에 대한 장기적인 경과 관찰과 세심한 심혈관계 기능에 대한 평가가 필요하다.

주요어: 폐동맥 고혈압, 기관지폐이형성증, 미숙아

학번: 2013-22595

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