Myocardial performance index by tissue Doppler in bronchopulmonary dysplasia survivors

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Bronchopulmonary dysplasia (BPD) survivors from the surfactant era were evaluated by echocardiography in a few studies and no significant differences were found between BPD and non-BPD children. In this study, we evaluated these children with myocardial performance index (MPI), which was obtained by tissue Doppler echocardiography (TDE) in addition to the conventional methods. Fifteen children with BPD who did not have any cardiopulmonary symptoms at the time of the study were examined. All children were studied with M-mode, two-dimensional and DE. Pulmonary artery systolic pressures (PAPs) were estimated from tricuspid regurgitant velocity, and MPI for both ventricles were obtained by TDE. Results were compared with those of term-born, age- and sex-matched control children. While the variables obtained by M-mode and DE did not differ between the groups, the right and left ventricular MPI were found to be significantly higher in the BPD group compared with the control group (mean right ventricular MPI 0.48±0.04 vs. 0.41±0.05; mean left ventricular MPI 0.47±0.05 vs. 0.39±0.06). In addition, mean PAPs values of the patients were found to be significantly higher than those of the controls (30.4±6.9 mmHg vs 23.3±5.3 mmHg), and there was a positive correlation between PAPs and right ventricular MPI values in the BPD group (r=0.5). While routine echocardiographic examinations revealed no difference between the groups, MPI measurements by TDE technique yielded significantly higher values in the BPD group. To this extent, our study is the first to show that survivors of BPD may, in fact, have a subclinical ventricular dysfunction.

Key words: bronchopulmonary dysplasia, myocardial performance index, Tei index, tissue Doppler echocardiography.

With the introduction of new therapies in peri- and neonatology, a changing pathology and clinical course of bronchopulmonary dysplasia (BPD) have been recognized. The consequences of this "new BPD" are of interest.

Thus far, most studies concerning the long-term prognosis of these infants have focused primarily on airways disease. However, those infants with BPD are also at high risk of cardiovascular sequelae as well, and most of the published studies on the cardiovascular outcome in preterm children with BPD date from the era before surfactant and comprise symptomatic patients on oxygen supplementation[1-5].

The aim of this study was to evaluate cardiovascular findings of clinically asymptomatic BPD survivors born during the surfactant era. For this purpose, after evaluating by M-mode, two-dimensional (2D) and Doppler echocardiography (DE), we used myocardial performance index (MPI) to assess global cardiac functions, which was proposed by Tei and coworkers in 1995[6]. In this study, instead of the method that was originally defined by Tei and coworkers, the MPI was obtained by tissue Doppler echocardiography (TDE), which is a newly introduced technique in routine practice echocardiography.

Material and Methods

The study population was derived from 15 children who were born prematurely and admitted to the same neonatal intensive care unit between 1998 and 2003. All the children in the study group had developed BPD following respiratory distress syndrome and received postnatal steroid therapy according to our institutional protocol[7]. Criteria for BPD diagnosis were: the need for ventilator dependence, oxygen supplementation, or both, at or beyond the first 28 days of life combined with radiographic evidence of lung disease[8]. Patients having major congenital malformations, intrauterine infections, sepsis, or inherited metabolic diseases were excluded. All the children in the study group were older than 12 months of age and had been free of cardiopulmonary symptoms for at least the last six months prior to the study.

The comparison group was comprised of 15 healthy children who were admitted to our outpatient clinics for health maintenance. They were matched with the study subjects for gender and age.

The study was approved by the Committee of Ethics for the Medical, Surgical and Drug Researches of our institution, and informed parental consent was obtained.

A complete physical examination was performed. Evaluation of the cardiopulmonary system included respiratory rate, heart rate, blood pressure, oxygen saturation (Nellcor NPB-290), and blood hemoglobin level.

None of the children was acutely ill or taking medications at the time of the study. All had a normal hemodynamic state and were normally hydrated during the echocardiographic study.

All children were in sinus rhythm and had a normal electrocardiographic pattern.

Transthoracic echocardiography was performed with the subject in the supine position using a Vingmed System V ultrasound system (G-Vingmed, Horten, Norway). The scanning was performed using a 3.5 MHz probe from the parasternal, apical, sub- and supracostal windows to obtain measurements and to ensure that there were no anatomical abnormalities in the heart[9]. The same pediatric cardiologist performed all the echocardiographic examinations. During the echocardiographic studies, patients were sedated by chloral hydrate with a single dose of 75 mg/kg orally[10,11].

M-mode recordings were used to measure cardiac dimensions, including left ventricular end diastolic and end systolic dimensions (LVED and LVES, respectively), thickness of the interventricular septum and thickness of the left ventricular posterior wall at end diastole and at end systole[12,13]. Left ventricular dimensions were normalized for body size by dividing the variables by the body surface area.

Left ventricular shortening fraction was calculated using the formula "(LVED-LVES)/ LVED x 100", and ejection fraction (EF) was calculated using volumetric methods. Measurements of right and left ventricular preejection period (PEP), ejection time (RVET, LVET) and systolic time interval ratios were performed as previously described[14]. At least three consecutive ventricular systoles were examined to give the mean systolic time intervals for each ventricle. An electrocardiogram with a well-defined QRS wave was simultaneously recorded.

Ventricular diastolic filling patterns were assessed by pulsed wave Doppler flow across the mitral and tricuspid valves. A single lead electrocardiogram was recorded simultaneously, and phases of respiration were differentiated with a respiration probe. Each measurement was made three times at end expiration for all positions and mean values were obtained. Peak velocities of E-wave and atrial A-wave were recorded for transmitral and transtricuspid flows, and the ratio of early diastolic to late diastolic velocity was derived. The acceleration time, deceleration time and total duration of diastolic filling for each ventricle were recorded[15,16].

For measuring pulmonary artery systolic pressure (PAPs), peak velocity of the tricuspid regurgitant jet was identified by continuous-wave Doppler ultrasound. To derive a systolic transtricuspid gradient, modified Bernoulli equation was used. Right atrial pressure was estimated clinically from the jugular veins[17].

Adjusting the echocardiography equipment to tissue Doppler measurements, the following major velocity time integrals for each ventricle were obtained (by placing the cursor to the

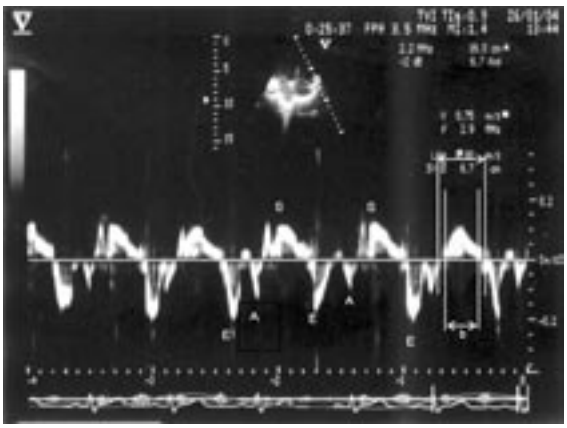

Fig. 1. Tissue Doppler echocardiography-derived time intervals for calculating ventricular myocardial performance index (MPI). The *a* is the atrioventricular valve closing-to-opening time. Time interval *b* is ejection time of ventricles. (A: Mitral or Tricuspid A wave. E: Mitral or tricuspid E wave. S: Ejection of ventricles. MPI = (a-b) / b = (IVCT + IVRT) / ET).

ventricle's muscle close to the annular region) as previously described: isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ET[18]. Measurements were made in three cardiac cycles, and the average was calculated for MPI analysis. The MPI is defined as the sum of IVCT and IVRT divided by the ET. Measured intervals are depicted in Fig. 1.

Data were expressed as mean value ± SD or medians and ranges. Clinical variables and echocardiographic measurements of the two groups were compared by using the unpaired Student's t-test, if appropriate, and the Mann-Whitney U test was used for the data that were not normally distributed. Statistical relationships between the MPI and duration of ventilator and oxygen supplementation therapy were assessed by the Spearman correlation analysis, and the statistical relationships between the MPI and PAPs were assessed with Pearson correlation analysis. A difference was considered significant at $p<0.05$.

Results

A total of 15 children with BPD and 15 healthy full-term children were studied. The mean duration of ventilator dependence and oxygen supplementation for BPD children was 104.4 ± 91.3 days (range: 46–334 days), and at the time of the study, patients had been free of cardiopulmonary symptoms for a mean period of 35.7 ± 13.7 months (range: 9.4–57.2 months).

Children with BPD were significantly lighter and less mature at birth than the children in the control group (birthweight 1030 ±

Table I. Comparison of Physical Examination, Oxygen Saturation and Hemoglobin Concentration of the BPD and Control Groups at the Time of Examination

	BPD (n=15)	Control (n=15)	p
Age (months)[a]	39.1 ± 13.3 (13–63)	40.3 ± 13.0 (10–59)	>0.05
Weight (kg) [a]	12.28 ± 2.95 (7.0–18.0)	15.07 ± 2.77 (8.50–18.35)	<0.05
Height (cm) [a]	91.6 ± 11.0 (69–109)	97.5 ± 9.6 (74–109.5)	>0.05
Oxygen saturation (%) [b]	98 (95–100)	98 (98–100)	>0.05
Systolic blood pressure (mmHg) [b]	90 (90–110)	100 (70–110)	>0.05
Diastolic blood pressure (mmHg) [b]	50 (50–60)	60 (50–65)	>0.05
Heart rate (pulse/minutes) [a]	100.2 ± 13.0 (80–120)	103.2 ± 12.1 (75–120)	>0.05
Respiration rate (breath/minutes) [b]	32 (22–40)	30 (28–33)	>0.05
Hemoglobin concentration (g/L) [a]	121 ± 8.0 (105–135)	118 ± 8.0 (105–136)	>0.05

BDP: bronchopulmonary dysplasia

[a] Data are expressed as means ± SD (range) - [b] Data are expressed as medians (range)

283 g (range: 600–1500 g) vs. 3216 ± 339 g (range: 2700–3900 g), respectively, $p<0.05$; gestational age 27.3 ± 1.8 weeks (range: 24–30.5 weeks) vs. 38.9 ± 0.9 weeks (range: 38–40 weeks), respectively, $p<0.05$). At the time of the assessment, children with BPD were still significantly lighter than term control children (12.28 ± 2.95 kg vs. 15.07 ± 2.77 g, respectively, $p<0.05$). When height was analyzed, the mean height of the subjects with BPD was lower than that of the normal control subjects; however, there was no statistical difference between the groups in terms of

Table II. Comparison of Left Ventricular Systolic and Diastolic Functions of BPD and Control Subjects

	BPD (n=15)	Control (n=15)	p
LVED / BSA (mm/m^2)[a]	54.9 ± 6.2 (42.8–67.5)	51.2 ± 4.6 (44.5–58.6)	>0.05
LVES / BSA (mm/m^2)[a]	33.1 ± 5.3 (24.5–43.1)	31.4 ± 3.8 (24.1–37.9)	>0.05
IVSs / BSA (mm/m^2)[a]	12.9 ± 2.3 (8.3–16.7)	12.3 ± 2.4 (8.9–17.4)	>0.05
IVSd / BSA (mm/m^2)[a]	8.8 ± 2.1 (5.7–12.1)	8.1 ± 1.7 (5.3–10.7)	>0.05
LVPWd / BSA (mm/m^2)[a]	8.3 ± 1.4 (6.3–10.6)	7.3 ± 1.5 (4.8–10.0)	>0.05
LVPWs / BSA (mm/m^2)[a]	13.5 ± 1.9 (9.4–17.1)	12.8 ± 1.4 (10.8–15.2)	>0.05
EF (%)[a]	71.9 ± 4.7 (65–79)	70.8 ± 3.9 (66–80)	>0.05
LVSF (%)[b]	40.1 (35–46)	39 (35–47)	>0.05
PEP (msec)[a]	59.6 ± 12.6 (41–81)	60.7 ± 12.1 (40–76)	>0.05
LVET (msec)[b]	256 (190.5–297)	256 (166–286)	>0.05
PEP/LVET[a]	0.24 ± 0.05 (0.16–0.32)	0.24 ± 0.05 (0.17–0.32)	>0.05
Mitral E (cm/sec)[a]	1.0 ± 0.1 (0.8–1.0)	1.1 ± 0.2 (0.8–1.1)	>0.05
Mitral A (cm/sec)[a]	0.7 ± 0.2 (0.44–1.02)	0.7 ± 0.1 (0.49–1.07)	>0.05
E/A[a]	1.6 ± 0.4 (1.0–2.4)	1.6 ± 0.4 (1.0–2.4)	>0.05
AT (msec)[a]	78.7 ± 15.0 (57–105.7)	78.9 ± 12.4 (64.5–107.0)	>0.05
DT (msec)[b]	105.8 (72.5–207)	120.5 (86–149)	>0.05
TDF (msec)[b]	260.5 (187–619)	286.0 (226–411)	>0.05
Heart rate (pulse/minute)[a]	104.9 ± 21.9 (61–133)	102.1 ± 13.1 (82–130)	>0.05

[a]Data are expressed as means ± SD (range) [b] Data are expressed as medians (range)
LVED: Left ventricular end diastolic diameter. BSA: Body surface area. LVES: Left ventricular end systolic diameter. IVSs: Thickness of interventricular septum at end systole. IVSd: Thickness of interventricular septum at end diastole. LVPWd: Left ventricular posterior wall thickness at end diastole. LVPWs: Left ventricular posterior wall thickness at end systole. EF: Ejection fraction. LVSF: Left ventricular shortening fraction. PEP: Preejection period. LVET: Left ventricular ejection time. Mitral E: Mitral E wave. Mitral A: Mitral A wave. AT: Acceleration time of the E wave. DT: Deceleration time of the E wave. TDF: Total diastolic filling time.

Table III. Comparison of Right Ventricular Systolic and Diastolic Functions of the BPD and Control Subjects

	BPD	Control	p
PEP (msec)[a]	58.6 ± 11.4 (43–81)	65.2 ± 8.8 (53–86)	>0.05
RVET (msec)[b]	264 (188–338)	278 (216–326)	>0.05
PEP/RVET[a]	0.22 ± 0.04 (0.17–0.30)	0.24 ± 0.04 (0.18–0.30)	>0.05
Tricuspid E (cm/sec)[b]	0.70 (0.52–1.21)	0.60 (0.47–0.84)	>0.05
Tricuspid A (cm/sec)[a]	0.6 ± 0.2 (0.35–0.92)	0.6 ± 0.1 (0.33–0.88)	>0.05
E/A[b]	1.1 (0.9–1.7)	0.99 (0.9–1.9)	>0.05
AT (msec)[b]	93.0 (66–147)	98.7 (81.5–155.7)	>0.05
DT (msec)[a]	117.2 ± 33.4 (62–193.7)	118.9 ± 23.7 (90.5–165.7)	>0.05
TDF (msec)[b]	248.8 (201–592.5)	291.5 (192.5–490)	>0.05
Heart rate (pulse/minute)[a]	106.4 ± 20.2 (63–130)	100.9 ± 17.8 (69–136)	>0.05

[a]Data are expressed as means ± SD (range), [b]Data are expressed as medians (range)
PEP: Preejection period. RVET: Right ventricular ejection time. Tricuspid E: Tricuspid E wave. Tricuspid A: Tricuspid A wave. AT: Acceleration time of E wave. DT: Deceleration time of E wave. TDF: Total diastolic filling time.

height (91.6 ± 11.0 cm vs. 97.5 ± 9.6 cm, p>0.05). The study groups did not differ with respect to gender and age at the time of the examination, and 93.3% of the children in both groups were older than two years of age (Table I).

Children with BPD and control subjects did not differ significantly with respect to heart rate, respiratory frequency, systolic and diastolic blood pressure, hemoglobin concentration, and oxygen saturation (Table I).

Mild mitral valve regurgitation was found in one BPD and two control subjects (3.5 m/sec and 4.1 m/sec, 3.8 m/sec, respectively) with no other abnormal cardiac findings. There was no significant pulmonary regurgitation in any of the patients or control subjects.

M-mode, 2D and Doppler-derived variables and ratios, which were used to evaluate systolic and diastolic functions of ventricles, did not show significant differences between the BPD and the control group (Tables II and III).

Left ventricular TDE-derived time intervals (IVCT, IVRT and ET) did not differ significantly between the BPD and the control subjects. However, left ventricular MPI was significantly increased in BPD patients compared to control subjects (0.47 ± 0.05 vs. 0.39 ± 0.06 respectively, p<0.05). When the right ventricular TDE-derived time intervals were evaluated, IVRT was found to be significantly prolonged in the BPD group in comparison with the control group (52.5 ± 8.6 msec vs. 45.6 ± 5.8 msec, respectively, p<0.05). However, ET and IVCT did not differ significantly between the groups. In addition, right ventricular MPI was also significantly increased in BPD patients compared to control subjects (0.48 ± 0.04 vs. 0.41 ± 0.05, respectively, p<0.05) (Table IV).

There were no significant correlations between the right/left MPI and the duration of ventilator dependence and oxygen supplementation therapy.

Tricuspid regurgitant jet was detected in 11 children (73%) in the BPD group and in 13 children (87%) in the control group. Mean PAPs was significantly higher in BPD patients compared with control subjects (30.4 ± 6.9 mmHg (range: 21–41 mmHg) vs. 23.3 ± 5.3

Table IV. Comparison of Right and Left Ventricular Functions of BPD and Control Subjects by Tissue Doppler Echocardiography

		BPD	Control	p
IVRT (msec)	Right[a]	52.5 ± 8.6 (39–66.8)	45.6 ± 5.8 (38–58.5)	<0.05
	Left[a]	51.0 ± 6.1 (45.0–66.2)	46.2 ± 10.4 (31.0–68.3)	>0.05
IVCT (msec)	Right[b]	52.3 (44.3–81.3)	59 (41.5–70.5)	>0.05
	Left[b]	54 (44.0–67.0)	52 (42.3–62.0)	>0.05
ET (msec)	Right[b]	220.5 (282.5–391.7)	247.7 (292.5–400)	>0.05
	Left[b]	220.3 (186.5–285.6)	258.5 (162.5–280.8)	>0.05
Heart rate (pulse/minute)	Right[a]	108.9 ± 17.2 (80–133)	102.8 ± 16.7 (78–137)	>0.05
	Left[a]	111.3 ± 18.3 (78–136)	97.6 ± 16.5 (78–125)	>0.05
Myocardial Performance Index (Tei index)	Right[a]	0.48 ± 0.04 (0.40–0.56)	0.41 ± 0.05 (0.34–0.50)	<0.05
	Left[a]	0.47 ± 0.05 (0.38–0.54)	0.39 ± 0.06 (0.29–0.54)	<0.05

[a] Data are expressed as means ± SD (range)
[b] Data are expressed as medians (range)
IVRT: Isovolumetric relaxation time. IVCT: Isovolumetric contraction time. ET: Ejection time.

mmHg (range: 14–30 mmHg), respectively, $p<0.05$). There was a positive correlation between the right ventricular MPI and PAPs ($r=0.5$, $p<0.05$), and no significant correlation was found between left ventricular MPI and PAPs.

Discussion

Few studies have examined the cardiovascular follow-up of BPD survivors from the surfactant era. In the study by Farstad et al.[19], 13 children with BPD at 120 weeks' corrected age were evaluated by echocardiography and the M-mode-derived variables, and ratios did not show significant differences between the BPD and the control groups. However, DE indicated shortened pulmonary acceleration time in patients with the most severe peripheral pulmonary obstruction. A recent study by Korhonen et al.[20] had investigated the cardiovascular findings of very low birth weight school children with and without BPD. It was reported that all M-mode measurements were found to be within normal range and Doppler results did not differ between the BPD, no-BPD and term groups.

In the present study, in addition to M-mode, 2D and DE, we used TDE to calculate MPI. The index has been shown to be useful in the evaluation of ventricular function in various diseases, but its usefulness has not yet been evaluated in children who had BPD in the early months of life[6,21-26].

In the present study, when left ventricular dimensions (normalized for body size) and systolic functions were evaluated, no significant difference was found between the groups. In addition, the diastolic functions of both ventricles using transmitral and transtricuspid velocities were also evaluated, and no significant difference was found between the groups again. However, TDE-derived MPI was found to be significantly higher in the BPD group than the control group for both ventricles. Thus, consistent with the previous research findings, our data suggest that the index is more sensitive than the conventional methods in assessing overall cardiac function[22,26,27].

It had been shown that right ventricular MPI was prolonged significantly in patients with primary pulmonary hypertension[21]. Furthermore, in

the study by Kim et al.[27], left ventricular MPI of these patients was also found to be affected, while the left ventricular EF of the same patients was normal. The mechanism by which the left ventricular dysfunction occurs in primary pulmonary hypertension was explained by the right ventricular pressure overload, which causes a delay in early diastolic right ventricular pressure fall, resulting in leftward displacement of the interventricular septum, impaired left ventricular relaxation and filling in the early diastole[28-31]. Consequently, we suggested that the increased right ventricular MPI in our patients might be reflecting subclinical right ventricular dysfunction due to the long-standing right ventricular pressure overload that is seen in the natural course of the disease[32,33]. Presence of a positive relation between PAPs values and right ventricular MPI also supported this opinion. Furthermore, we suggested that the presence of right ventricular pressure overload was the reason for the increased left ventricular MPI in the study group. The increased left ventricular MPI with a normal EF in these patients was explained by the presence of subclinical left ventricular dysfunction.

In the present study, no evidence of pulmonary hypertension was found during the evaluation of patients by means of conventional methods. However, PAPs estimated from peak velocity of the tricuspid regurgitant jet was slightly elevated in BPD patients in comparison with the control subjects, and the difference was found to be statistically significant. Only three patients in the BPD group had borderline PAPs values (41 mmHg, 41 mmHg and 36 mmHg), while the rest had PAPs values within normal ranges (PAPs <35 mmHg). Even though there were no available data about the PAPs values of these children regarding the first few months of life, it is known that in BPD, PAP elevates in the natural course of the disease and returns to normal values over time[32-37]. Thus, consistent with this data, the slightly elevated PAPs values in our patients, most of which were in fact within normal ranges, suggested that these patients had developed pulmonary hypertension. We had seen that while PAPs of the BPD group was higher than that of the control group, pulmonary artery PEP/RVET ratios did not support this data. This can be attributed to the slight elevation in PAPs of the BPD group, which may not be enough to make a difference in the PEP/RVET ratio.

In the present study, MPI was determined by TDE. To the best of our knowledge, this study is the first to use TDE in measuring MPI in BPD survivors. Recent studies have shown that both methods of measuring MPI, TDE and conventional, correlate well with each other[38,39]. The conventional MPI has been reported to be independent of heart rate and blood pressure[6]. However, the inability to measure the interval between the end and onset of mitral/tricuspid flow and the ET simultaneously is a major limitation of conventional MPI. Due to this limitation, results are less reliable in the presence of physiologic heart rate changes. The TDE used in this study can simultaneously record systolic and diastolic mitral/tricuspid annular velocities. In contrast to the pulsed Doppler method, the time interval between the end and onset of diastolic annular velocities and the duration of the systolic wave can be measured in the same cardiac cycle. Thus, MPI by TDE may reduce inaccuracy due to heart rate fluctuation and has practical advantages over the conventional MPI[38-40].

In conclusion, we demonstrated that when the systolic and diastolic ventricular functions of clinically asymptomatic BPD survivors were compared with control subjects using routine echocardiographic techniques, no significant difference could be found between the two groups. However, with the use of TDE-derived MPI, we demonstrated the presence of a subclinical cardiac dysfunction in BPD survivors. Our data suggest that the index is more sensitive than the variables obtained by conventional methods in assessing subclinical cardiac dysfunction in BPD survivors.

As this study is the first to use the TDE-derived MPI to evaluate cardiac functions in asymptomatic BPD survivors, further studies are required to elucidate the utility of the index in this setting and to show the prognostic implications of our findings.

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